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Comparison of VCUG and DMSA scan in the detection of vesicoureteral reflux in children during first febrile urinary tract infection.

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Abstract

Objective: High-grade Vesicoureteral Reflux (VUR) is associated with the development of renal scar during febrile Urinary Tract Infection (UTI), subsequently leading to hypertension and chronic kidney disease in adulthood. This study was conducted to evaluate the diagnostic accuracy of Dimercaptosuccinic Acid (DMSA) scan during first febrile UTI in identifying VUR and predicting its severity.

Materials and methods: In this retrospective study, we enrolled children <12 years old with a diagnosis of first febrile UTI who had undergone both VCUG and DMSA scan in our hospital between 2005 and 2020. The sensitivity, specificity, positive and negative predictive values (PPV and NPV) of DMSA scan for detecting VUR was analyzed in all patients and across two age subgroups: ≤ 4 years old and >4 years old.

Results: A total of 208 patients (mean age: 3.34 ± 2.54 years old; male/female (M/F): 59/149) were enrolled. VUR was diagnosed in 261/416 rental units (62.7%) on VCUG. The sensitivity, specificity, PPV and NPV of DMSA scan in detecting VUR was as follows: 52%, 75%, 78% and 48%. After age-subgroup analysis, 158 patients were ≤ 4 years old (M/F: 51/107) and 50 patients were >4 years old (M/F: 8/42). The PPV and NPV for predicting VUR by DMSA scan was 85.6% and 46.3% in ≤ 4 years old and 55.5% and 56.2% in patients more than 4 years old.

Conclusion: The results of this study showed that using DMSA scan for the initial assessment of children with first febrile UTI alone, leads to missing many patients with high-grade VUR; thus, DMSA scan does not have enough accuracy for predicting VUR in comparison with VCUG.

Keywords: Vesicoureteral reflux, 99 mTC DMSA, Urinary tract infection.

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Introduction

Urinary Tract Infection (UTI) is a very common condition in pediatrics. Approximately 30%-40% of first febrile UTI episodes in children are associated with Vesicoureteral Reflux (VUR) [1]. High-grade VUR is associated with the development of renal scar, subsequently leading to hypertension and chronic kidney disease in adulthood [2]. Approximately 10-25% of patients with End-Stage Renal Disease (ESRD) who require dialysis and renal transplant suffer from reflux nephropathy [3]. For the appropriate management of VUR, early identification of the disease is essential; nevertheless, the best imaging modality with a high diagnostic ability for specifying the appearance of the kidney and indicating the presence of VUR is still not known.

Voiding Cystourethrography (VCUG) is the most popular and widely-used modality for VUR diagnosis in the "bottom-up" approach. However, VCUG is an undesirable procedure for the patient and family as it requires urethral catheterization and also fluoroscopic imaging, which exposes children to radiation [4]. In addition, it is capable of identifying clinically insignificant VURs that may never require attention. Dimercaptosuccinic Acid (DMSA) renal scan is used in the "top-down" approach to assess scar formation in patients diagnosed with VUR. It is also useful for detecting acute renal parenchymal involvement at the time of the febrile UTI.

Current evidence encourages the application of the "top-down" approach since a negative DMSA excludes the need for catheterization and a positive study detects the most at-risk patient population for subsequent renal scarring. On the other hand, a DMSA scan demands a visit to a tertiary medical center, placement of an intravenous line, sedation at some centers, and ultimately, higher health care expenditures [5,6]. The most important point, however, is whether a normal DMSA scan obviates the need for further investigation with VCUG. This study was conducted to evaluate the diagnostic

accuracy of DMSA scan during first febrile UTI in identifying VUR and predicting its severity.

Materials and Methods

In this retrospective study, we included children <12 years old with a diagnosis of first febrile UTI who had undergone both VCUG and DMSA scans at Labbafinejad medical center between 2005 and 2020. The diagnosis of febrile UTI was based on the presence of fever and positive urine culture, defined by culture of ≥ 105 colony-forming units⁄ml of a single microorganism in a sample obtained *via* catheterization, urine bag or clean voided midstream urine from toilet-trained children. In all patients, renal DMSA scan was performed within the first two weeks of UTI presentation and VCUG was performed at the first month after treating the infection. Patients with the following characteristics were excluded from the study: Renal duplex system, malrotation anomalies, ectopic kidney, multicystic dysplastic kidney, polycystic kidney, single kidney, ureterocele, or bladder diverticulum and kidney stone. This study followed the tenets of the deceleration of Helsinki and was approved by local institutional review board.

A radiologist determined VUR grade on patients' first VCUG according to the classification system of the international reflux study committee [7]. High-grade VUR was defined as reflux grade three or more. Also, based on the DMSA scan, renal parenchymal involvement was classified and reported as normal (no change), pyelonephritic change, scars and atrophy. The VCUG and DMSA scans were additionally evaluated and reported by another two nuclear medicine radiologists who were blinded to the results reported by the first radiologist.

All data was analyzed across two age subgroups: ≤ 4 years old and >4 years old. The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of DMSA scan for predicting VUR were assessed. Qualitative and quantitative data are presented as frequency (%) and mean ± SD, respectively. Categorical and quantitative variables were compared using the chi-square test and ANOVA test, respectively. Spearman test was used to assess the correlation between VUR grade and severity of renal damage on DMSA scan. All statistical analysis was performed using SPSS version 20 (IBM SPSS Inc., Chicago, IL). A $p<0.05$ was considered statistically significant. This study was approved by medical ethics committee of urology and nephrology research center in Shahid Beheshti university of medical sciences, Tehran-Iran, with following number: IR. SBMU.UNRC.1395.10.

Results

During the study period, 1500 children had a diagnosis of first febrile UTI. Out of these, 208 patients who had undergone both imaging studies met the inclusion criteria and were included in the final analysis. The overall male-to-female (M/F) ratio was 0.39 (59/208 were males). The mean age ± SD of patients was 3.34 ± 2.54 years old (range: 1 month-12 years). According to the VCUG results, VUR was present in 261/416 renal units (62.7%). VUR was not detected in 18/59 males (30.9%) and 54/149 females (36.2%) in the VCUG study (p=0.518). Regarding VUR grade, 37/59 male (62.7%) and 75/149 female patients (50.3%) demonstrated high-grade VUR in the VCUG study (p=0.34).

After performing age-subgroup analysis, 158 patients were ≤ 4 years old (M/F: 51/107) and 50 patients were >4 years old (M/F: 8/42). The incidence of high-grade VUR was not significantly different between the two age groups (172/316 renal units in ≤ 4 years old *vs.* 37/100 renal units in >4 years old; p=0.08). Table 1 shows the results of VCUG and DMSA scans across the two age subgroups. The PPV and NPV of DMSA scan for predicting VUR was 85.6% and 46.3% in ≤ 4 years old and 55.5% and 56.2% in patients above 4 years old.

Total		**Age ≤ 4 Years**	**Age>4 Years**
Total renal unit	416	316	100
Sex (Male/ Female)	59/149	51/107	8/42
VCUG			
Normal	155 (37.3%)	103 (32.5%)	52 (52%)
Grade I	20 (4.8%)	15 (4.7%)	5 (5%)
Grade II	32 (7.7%)	26 (8.2%)	6 (6%)
Grade III	117 (28.1%)	88 (27.8%)	29 (29%)
Grade IV	57 (13.7%)	50 (15.8%)	7 (7%)
Grade V	35 (8.4%)	34 (10.7%)	1 (1%)
DMSA scan			
Normal	241 (57.9%)	177 (56.01%)	64 (64%)
Pyelonephritic change	44 (10.6%)	36 (11.4%)	8 (8%)
Scar	106 (25.5%)	81 (25.6%)	25 (25%)
Atrophy	25 (6%)	22 (6.7%)	3 (3%)

Note: Data is presented as frequency (%) for qualitative and mean ± SD for quantitative data.

VCUG: Voiding Cystourethrogram; DMSA: Dimer Captosuccinic Acid Scan.

Table 1. Clinical and imaging findings in the total study population and across the age subgroups (total number of patients=208).

DMSA scan was reported normal in 124/261 (47.5%) renal units that had been diagnosed as VUR on VCUG and in 88/209 (42.1%) renal units, which had been diagnosed as high-grade VUR. DMSA scan showed abnormality in 72/113 (63.7%) patients who were diagnosed with high-grade VUR on VCUG. Also, out of 23 patients with low-grade VUR on VCUG, an abnormal DMSA scan was seen in only 8 patients (34.7%). On the other hand, DMSA scan indicated abnormal changes in 38 renal units that did not show VUR on VCUG.

The findings of DMSA scans are presented in Table 2 based on VUR grade on VCUG. The sensitivity, specificity, PPV and NPV of DMSA scan in predicting VUR was as follows: 52%, 75%, 78% and 48%. As renal cortical damage increased from pyelonephritic change to scar formation, the rate of high-grade

VUR also increased significantly (p=0.001). Compared with other subgroups of parenchymal involvement on DMSA scan, patients with pyelonephritic change had a significantly higher rate of grade III VUR (p<0.001) and patients with renal scarring had a significantly higher rate of grade IV-V VUR (p=0.005).

Renal parenchymal involvement on DMSA				
	Normal	**Pyelonephritic change**	**Scar**	**Atrophy**
VUR grade on VCUG				
Normal	117 (28.1%)	14 (3.3%)	19 (4.5%)	5 (1.2%)
Grade I	12 (2.8%)	3 (0.7%)	5 (1.2%)	0 (0%)
Grade II	24 (5.8%)	4 (0.9%)	3 (0.7%)	1 (0.2%)
Grade III	63 (15.1%)	18 (4.3%)	29 (6.9%)	7 (1.7%)
Grade IV	18 (4.3%)	5 (1.2%)	28 (6.7%)	6 (1.4%)
Grade V	7 (1.7%)	0 (0%)	22 (5.2%)	6 (1.4%)

Note: Data is presented as frequency (%).

VCUG: Voiding Cystourethrogram; DMSA: Dimercaptosuccinic Acid; VUR: Vesicoureteral Reflux

Table 2. Correlation between DMSA scan findings and grade of reflux in VCUG.

Discussion

Childhood UTI management strategies aim to prevent permanent renal scarring and ultimately, to decrease the risk of developing hypertension, proteinuria, hyposthenuria or renal failure in the future. Although it is evident that early detection and treatment of VUR is the way to achieve this goal, the most appropriate strategy that leads to early and accurate diagnosis of VUR remains controversial. Conventionally, renal ultrasound was used to determine the presence of upper tract dilation and VUR after the first febrile UTI episode in children. Ultrasound evaluation did not carry a risk of radiation exposure; however, further studies questioned its efficacy.

In a review of 42 studies, Shaikh, et al. [8] compared the diagnostic accuracy of DMSA scan and renal ultrasound with VCUG in children less than 19 years of age, concluding that renal ultrasound is not accurate enough for detecting different grades of VUR and emphasizing the important role of more specialized studies such as radiographic VCUG and DMSA. Also, Bush, et al. [9] did not suggest renal ultrasound following first febrile UTI due to its poor sensitivity (34%) and limited positive predictive value (47%). On the contrary, Fuente and colleagues evaluated 155 patients with their first episode of febrile UTI who were below 2 years of age and concluded that renal ultrasound can be used as a screening method for VUR [10].

They also advised against the use of VCUG or DSMA in children with a normal renal ultrasound and suggested that VCUG should be performed only in patients with abnormal findings in renal ultrasound or in those with recurrent UTI. DMSA scan, which is currently the gold-standard study for assessing acute renal inflammation and established renal scarring, has replaced the intravenous urogram. DSMA is able to detect renal involvement after a febrile UTI and can thus indicate that the kidneys are at risk of subsequent injury. One of the major disadvantages of the “top-down” approach is that it will miss children with VUR in whom renal involvement is not evident [11].

In the study, the rate of a normal DMSA scan in patients with VUR identified by the VCUG was significant. In a previous prospective study, the sensitivity and specificity of acute phase DMSA scan for detection of VUR were 95.7% and 71.9%, respectively [3]. In another prospective study, sensitivity, specificity, PPV and NPV of DMSA scan for prediction of VUR were 71%, 58%, 44% and 81%, respectively [12]. In another study by Tseng et al., DSMA scan had 71% sensitivity, 58% specificity, 44% PPV and 88% NPV for predicting VUR [5]. Similarly, Camacho and colleagues reported 48% PPV and 88% NPV for prediction of VUR by DMSA scan [13]. In this results showed sensitivity of 52% and specificity of 75% for VUR prediction by DMSA scan. Also, in our study, DSMA had 78% PPV and 48% NPV.

These differences might be due to variations in the nature and design of these studies and also, as a tertiary center, our patients may not be a good representative of the entire population. In a study on 523 children aged 2 years old or less with febrile UTI, Zhang, et al. [14] reported a sensitivity of 96.15% and a PPV of 34% for predicting VUR with DMSA scan in children <6 months old. They concluded that DMSA scan could be used as an effective screening tool to identify patients who are likely to have dilating VUR and UTI recurrence. In another study, Sorkhi, et al. [12] divided children into three age groups of less than 2 years old, 2-5 years old and more than 5 years old; DMSA scan had a PPV of 41.2% and a NPV of 81.8% for prediction of VUR in children less than 2 years old.

This study found a PPV and NPV of 85.6% and 46.3%, respectively, for VUR detection in patient’s ≤ 4 years old, whereas in patients above 4 years of age the PPV and NPV were 55.5% and 56.2%. These differences might be attributable to the different age groups as well as the nature and design of these two studies. Altogether, the results of these studies should be interpreted with caution. In the present study, DMSA scan showed abnormal changes only in 34.7% of patients with low grade VUR, while abnormal changes were significantly more present in high grade VUR. Thus, DMSA scan does not seem to be an accurate test for identifying low grade VUR in children with a first febrile UTI. In a retrospective study evaluating 303 patients diagnosed with first febrile UTI, Hansson, et al. [15] found that abnormal DMSA scans were strongly associated with high grade VUR (p≤0.001).

Likewise, Herz, et al. indicated that initial DMSA scan could predict clinically significant reflux after studying 121 children with febrile UTI [3]. Historically, it was mistakenly believed that every VUR should be diagnosed and treated to prevent

UTI and minimize the risk of renal damage. Nowadays, however, it is generally accepted that patients at low-risk of renal damage and recurrent UTI can be managed expectantly, while antibiotic prophylaxis and surgical correction should be offered to the high-risk population [3,16]. In the evaluation of pediatrics with febrile UTI, the ultimate goal is to identify patients at risk of recurrent UTI and renal injury, and not simply detecting VUR [17]. Based on our study, in which DMSA scan demonstrated abnormal changes only in 42.1% of patients with high grade VUR in VCUG, a significant number of patients with not only low-grade but also high-grade VUR would have been missed if the "top-down" approach was to be used.

Thus, the "top-down" approach alone does not seem to be a good choice for the management of children with febrile UTI, based on our results. In 38 renal units, we detected abnormal changes in DMSA scan while VCUG study was negative for VUR. In a study on 100 children aged up to one year with a first febrile UTI, Pokrajac, et al. [18] aimed to investigate whether VUR was associated with evolution to renal scarring (detected by DMSA scan) following febrile UTI in infants; DSMA scan detected acute pyelonephritis in 66% of the patients but only 33.3% had VUR. In children with renal scars, VUR was observed in 50% of the cases. Therefore, they concluded that the pathogenesis of renal scarring after febrile UTI in young children is multifactorial and the presence of VUR increases the risk of developing pyelonephritis and renal scarring.

In fact, they showed the important role of the "top-down" approach in the management of children with first febrile UTI. It should be noted that parenchymal defects might be seen on DMSA scans in the absence of a previous UTI. In this case, the defects may be attributed to congenital dysplasia rather than renal damage occurring after infection or VUR. Nevertheless, discrimination between secondary and congenital parenchymal defects cannot be solely made based on DMSA findings. Hansson, et al. [15] showed that 46% of their studied population who had a diagnosis of renal parenchymal affection on DMSA scan did not have a demonstrable reflux on VCUG. As VUR may occur intermittently, cyclic VCUG can enhance the ability of this method to detect reflux and is thus recommended in suspicious cases with only one negative VCUG study.

A study by Papadopoulou, et al. [19] that assessed 275 children younger than 2 years who underwent two cycles of VCUG found that intermittent VUR occurred in up to 23% of children undergoing VCUG. Thus, in the current study, cyclic VCUG might be able to detect VUR in the 38 renal units with abnormal changes in DMSA scan but a normal VCUG. The amount of radiation exposure, which is considered as one of the other disadvantages of the "top-down" approach, frequently concerns children's parents. Some of the well-known side effects of radiation exposure include secondary malignant neoplasms and gonadal damage, particularly in the pediatric population. Gonadal dosimetry is higher for DMSA renal scans (effective dose, 1.8 mSV; ovary, 85 mrads; testis 45 mrads) in comparison to continuous fluoroscopic cystography (effective dose, 0.45 mSv) [20].

Compared to fluoroscopy, which is frequently used for VCUG studies, DMSA has a 5–10 fold higher radiation dose [3,21]. This becomes more important in patients who need to repeat these imaging evaluations. Besides radiation exposure, economic burden, availability, requirement of an intravenous access and/or sedation in some centers, delay in treatment initiation and inconsistency in interpretation of its results are some other limitations of a DMSA scan as an alternative modality following first febrile UTI in children [17]. The results of DMSA scan depend on the experience of the reporting physician. Matoo, et al. [22] evaluated the inter-observer variability in the interpretation of DMSA scans in the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial.

They compared the reports of DMSA scans for acute pyelonephritis and renal scarring obtained from reference and non-reference radiologists, and concluded that many factors seem to affect inter- and intra-observer variability, including expertise of the reporting radiologist, inadequate attention to published guidelines for detailed reporting, severity of renal damage, the specific techniques used for the procedure, and also the presence of any previous comparative study. In the RIVUR trial, a significant inter-observer variability was observed in the reporting of abnormal DMSA scans, emphasizing the need to optimize the clinical yield of DMSA renal scans by developing novel guidelines for standardized interpretation of results.

Conclusion

This study showed that the use of DMSA renal scans in the initial assessment of children with a first episode of febrile UTI, alone, may result in missing many patients with high-grade VUR and that DMSA scan could not predict results of VCUG with enough accuracy. Further prospective studies are warranted to draw a definite conclusion. The main limitation of our study is its retrospective design. On the other hand, the strengths of this study include a relatively high sample size in a single center study and blinding of physicians to the results of VCUG.

Conflicting Interests

None declared.

Funding

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Ethical Approval

The study group adheres to the principles of medical ethics introduced by the health ministry and the declaration of Helsinki and legislation in the medical ethics committee of urology and nephrology research center in Shahid Beheshti

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Informed Consent

Written informed consent was obtained from all subjects before the study.

Contribution

FS and BN project administration and conceptualization, MD and MS writing original draft, methodology and investigation, NB formal analysis and data curation, MA and HR writing-review and editing, investigation and data curation.

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