DMSA taraması: Tekrarlayan İdrar Yolu Enfeksiyonu Olan Çocuklarda Başlangıç Tetkiki Olabilir mi?

DMSA Scan: May It Be the Initial Investigation in Children with Recurrent Urinary Tract Infections?

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ÖZ

GİRİŞ ve AMAÇ: *Vezikoüreteral reflü (VUR) renal parankimal hasara neden olan önemli bir anomalidir. Voiding sistoüretrografi VUR araştırılmasında standart tanı yöntemidir. Gereği olmayan VCU incelemesinden kaçınmak için teknesyum 99m DMSA böbrek taraması önerilmektedir. Bu çalışmada tekrarlayan idrar yolu enfeksiyonu olup VCU incelemesi yapılan çocukların teknesyum 99m DMSA böbrek tarama sonuçları değerlendirilmiştir.*

YÖNTEM ve GEREÇLER: *Çalışmaya tekrarlayan idrar yolu enfeksiyonu olup böbrek ultrasonografi ve DMSA incelemesi yapılan 136 hasta dahil edilmiştir. Ultrasonografi ya da DMSA veya her ikisinin sonucunda anormallik olan ya da ultrasonografi veya DMSA normal olsa bile şikayetleri tekararlayan idrar yolu enfeksiyonu için tipik olan hastalara VCU incelemesi yapılmıştır.*

BULGULAR: *Bütün hastalar, VUR grubu (n: 46) ve VUR olmayan grup (n: 90) olarak VCU sonuçlarına göre iki gruba ayrılmışlardır. Sırasıyla; DMSA taramasının ve VCU ile yüksek derecede VUR saptananların duyarlılığı ve özgüllüğü %87.80 (%73.80-95.92) ve %42.11 (%32.04-52.67).*

TARTIŞMA ve SONUÇ: *Çalışmamızda, tekrarlayan İYE görülen çocuklarda VCUG'dan önce ilk tarama olarak DMSA taramasının yapılabileceğini öneriyoruz.*

Anahtar Kelimeler: *99m Tc dimerkaptosüksinik asit, tekrarlayan idrar yolu enfeksiyonu, voiding sistoüretrografi*

ABSTRACT

INTRODUCTION: *Vesicoureteral reflux (VUR) is an important anomaly that causes renal parenchymal damage. Voiding cystourethrography (VCUG) is the standard diagnostic method for detecting VUR. To avoid unnecessary voiding cystourethrography, a Technetium (Tc)-99-m-DMSA renal scan is recommended as the initial investigation. We aim to assess the association of abnormalities detected on dimercaptosuccinic acid (DMSA) scan with the presence of VUR on VCUG in children with recurrent urinary tract infections (UTI).*

METHODS: *A total of 136 patients with recurrent UTI underwent renal sonography and DMSA scan. VCUG was indicated if USG or DMSA or both were abnormal, or complaints were typical for recurrent UTI while USG or DMSA was normal.*

RESULTS: *All patients were divided into two groups according to their VCUG results as a VUR group (n: 46) and a non-VUR group (n: 90). The sensitivity and specificity of DMSA scan for the detection of high- grade VUR on VCUG was 87.80% (73.80-95.92%) and 42.11% (32.04-52.67%), respectively.*

DISCUSSION AND CONCLUSION: *We suggest that DMSA scan may be the initial investigation before VCUG in children with recurrent UTIs.*

Keywords: *99mTc dimercaptosuccinic acid renal scan, recurrent urinary tract infections, voiding cystourethrography*

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INTRODUCTION

The imaging evaluation of children with UTI aims to identify those with urinary tract anomalies such as vesicoureteral reflux (VUR) (1,2). VUR is a vital anomaly that causes renal parenchymal damage. Voiding cystourethrography (VCUG) is the standard diagnostic method for detecting VUR. Selective VCUG in children with UTI has been recommended for those with clinical risk factors such as younger age, recurrent UTI or abnormal results of other noninvasive imaging studies (3). Nevertheless, there are no uniform guidelines. Two different imaging approaches, i.e. "bottom-up and top-down" are preferred. The "bottom-up" approach utilizes ultrasonography followed by VCUG to detect possible VUR in children with a first febrile UTI, while the "top-down" approach uses with a screening DMSA scan followed by VCUG only in selected cases. Each approach has its own advantages and disadvantages. The bottom-up approach causes a high economic burden, radiation exposure and reluctance of patients whereas the top-down approach may possibly miss children with clinically significant VUR. A number of guidelines have been published regarding the imaging modalities to be utilized and exact protocol to be followed. However, there is still no consensus on the issue (4,5,6). Most guidelines nevertheless recommend the routine use of DMSA for evaluation of patients with recurrent UTI. In the present study, we aim to assess the association of abnormalities detected on DMSA scan with the presence of VUR on VCUG in children with recurrent UTI.

MATERIALS and METHODS

We retrospectively reviewed the medical records of children aged <18 years who underwent renal ultrasonography and DMSA then VCUG investigation for recurrent UTI at our hospital from August 2013 to August 2015. A total of 136 patients were enrolled in the study. Recurrent UTI was defined as having more than two episodes of UTIs as per the NICE guidelines. UTI was diagnosed if a child had positive nitrite and leukocyte esterase in a urine sample in the presence of typical symptoms including fever, loin tenderness, frequency, dysuria, cloudy urine or hematuria. All children also had at least one positive urine culture during the course of illness in addition to these criteria (6,7).

All children with recurrent UTI in the study underwent renal sonography and DMSA scan. VCUG was indicated if USG or DMSA or both were abnormal, or complaints were typical for recurrent UTI while USG or DMSA was normal. As a result, all the patients were divided into two groups according to their VCUG results: a VUR group (n: 46) and a non-VUR group (n: 90).

Technetium (Tc)-99-m-DMSA renal scan was performed according to the standard departmental protocol. Low-energy, high resolution, parallel-hole collimator was employed and adequate zoom, according to the child's size, was made. Multiple static images in posterior, right anterior oblique and left anterior oblique projections were acquired under dual-head digital gamma camera 3 hours after the intravenous administration of an average 100 megabecquerel (MBq) of 99-m-Tc-DMSA. A positive DMSA result was defined as scarring; focal or diffuse areas of reduced radionuclide uptake; large, small, or no kidneys; possible duplex kidney; or abnormal differential function (8,9).

Renal ultrasonography (USG) results of all patients were also evaluated. Hydronephrosis on USG was defined as a dilatation of the renal pelvicalyceal system according to the Society for Fetal Urology classification. Renal scar on USG was defined as an irregularity in the outline of kidney paired with the focal loss of renal pyramid and proximity of sinus echoes to the cortical surface (10).

VCUG was performed under aseptic measures by introducing a 6- or 8- Fr feeding tube into the bladder through the urethra. The urinary bladder was filled with non-ionic water-soluble contrast media injected via the feeding tube. Then a series of images were obtained to determine whether any liquid passed backward into one or both ureters when the patient emptied his or her bladder. A final image was obtained after the patient had voided completely to determine how well the bladder emptied. VUR was graded I to V on the basis of the criteria established by the International Reflux Study in Children. Grades I and II were regarded as low- grade VUR, while grade III-V were considered high-grade VUR (11).

Statistical Analysis

Histogram and q-q plots were examined, Shapiro-Wilk's test was applied to test the data

normality. Levene test was used to assess variance homogeneity. To compare the differences between groups, Pearson $\chi 2$ analysis was used for categorical variables or Mann-Whitney U tests were used for continuous variables. To assess the diagnostic performance of USG and DMSA on predicting VUR and high-grade VUR, Kappa statistic, sensitivity, specificity, positive predictive value and negative predictive values were calculated with 95% confidence interval. Analyses were conducted using Turcosa Cloud (Turcosa Ltd Co, Turkey) statistical software. A p value less than 5% was considered as statistically significant.

RESULTS

A total of 136 children (109 girls, 27 boys) were included. The mean age of the children was 7.0 (5.0-9.0) years old. Of the patients with recurrent UTI, 91 (66 %) had abnormal DMSA findings such as scarring, focal or diffuse areas of reduced radionuclide uptake; large, small, or no kidneys; possible duplex kidney; or abnormal differential function and 85 (62.5 %) had abnormal USG findings and 72 (52%) had abnormal findings both in DMSA and USG. VUR of any grade was diagnosed in 46 (33%) patients, 41 of had high-grade VUR.

The proportion of patients having hydronephrosis on renal sonogram or having scar/hypoactive area on DMSA scan or both varies significantly between the VUR and non- VUR groups.

Age, gender, results of urine culture, VUR, DMSA, USG findings were summarized in Table 1 and 2. The sensitivity and specificity of DMSA scan for detecting VUR on VCUG was 89.13%(76.43-96.38%) and 44.44%(33.96-55.30%), respectively. The positive and negative predictive values and positive and negative likelihood ratios were, 45.05%(34.60-55.84%), 88.89% (75.95-96.29%), 1.60(1.30-1.98) and 0.31(0.15-0.64) respectively.

The sensitivity and specificity of DMSA scan for the detection of high- grade VUR on VCUG was 87.80% (73.80-95.92%)and 42.11% (32.04-52.67%), respectively. The positive and negative predictive values were, 39.56% (29.46-50.36%), 88.89% (75.95-96.29%), respectively. The positive and negative likelihood ratios were for DMSA to rule out high- grade VUR on VCUG were 1.52(1.23-1.86), 0.29(0.12-0.68) respectively.

The sensitivity and specificity, the positive and negative predictive values, the positive and negative likelihood ratios both of USG and DMSA or the detection of high- grade VUR on VCUG were summarized in Table 3 as well.

Table 1. Comparisons of between groups

Variables	Groups		Total (*n*=136)	*p*
	VUR(+) (*n*=46)	VUR(-) (*n*=90)		
Age (yrs.)	6.0(4.0-9.0)	8.0(5.0-10.0)	7.0(5.0-9.0)	0.063
Sex				
Male	7(15.2%)	20(22.2%)	27(19.9)	0.333
Female	39(84.8%)	70(77.8%)	109(80.1)	
Kx				
E.coli	39(84.8%)	83(92.2%)	122(89.7)	0.233
Non E.coli	7(15.2%)	7(7.8%)	14(10.3)	
USG Findings				
Normal	7(15.2)	44(48.9)	51(37.5)	**<0.001**
Hydronephrosis, renal scar, atropyh	39(84.8)	46(51.1)	85(62.5)	
DMSA Findings				
Normal	2(4.3)	33(36.7)	35(25.7)	**<0.001**
Hypoactive area or scar	43(93.5)	51(56.7)	94(69.1)	
Agenesis	1(2.2)	6(6.7)	7(5.1)	
DMSA and USG Findings				
Present	36(78.3)	36(40.0)	72(52.9)	**<0.001**
Absent	10(21.7)	54(60.0)	64(47.1)	
Values are expressed as median(1st- 3rd quartiles) or n(%)				

Table 2. Findings on VCUG in 136 children with recurrent UTI

Findings	Number of children (%)
No VUR	**90 (66%)**
VUR	**46 (34%)**
Grade I-II	**5 (3%)**
Grade III-IV	**41 (31%)**

Table 3. Kappa Statistic and Statistical Diagnostic Measures Calculated to Assess the Predictive Performance of USG and DMSA in the presence of VUR/high-grade VUR

Marker	Statistical Diagnostic Measures						Kappa Statistic	
	SEN(95%CI)	SPE(95%CI)	PPV(95%CI)	NPV(95%CI)	PLR(95%CI)	NLR(95%CI)	K	*p*
VUR								
USG	84.78(71.13-93.66)	48.89(38.20-59.65)	45.88(35.02-57.04)	86.27(73.74-94.30)	1.66(1.31-2.10)	0.31(0.15-0.64)	0.279	**<0.001**
DMSA	89.13(76.43-96.38)	44.44(33.96-55.30)	45.05(34.60-55.84)	88.89(75.95-96.29)	1.60(1.30-1.98)	0.24(0.10-0.58)	0.271	**<0.001**
DMSA& USG	78.26(63.64-89.05)	60.00(49.13-70.19)	50.00(37.98-62.02)	84.38(73.14-92.24)	1.96(1.46-2.63)	0.36(0.20-0.64)	0.336	**<0.001**
High Grade VUR								
USG	85.37(70.83-94.43)	47.37(37.03-57.88)	41.18(30.61-52.38)	88.24(76.13-95.56)	1.62(1.29-2.04)	0.31(0.14-0.67)	0.251	**<0.001**
DMSA	87.80(73.80-95.92)	42.11(32.04-52.67)	39.56(29.46-50.36)	88.89(75.95-96.29)	1.52(1.23-1.86)	0.29(0.12-0.68)	0.222	**0.001**
DMSA&USG	78.05(62.39-89.44)	57.89(47.33-67.96)	44.44(32.72-56.64)	85.94(74.98-93.36)	1.85(1.39-2.47)	0.38(0.21-0.69)	0.296	**<0.001**

Values are expressed as estimates and 95% confidence intervals. SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, CI: Confidence interval

DISCUSSION

Vesicoureteral reflux is a crucial anomaly that causes renal injury in children with UTI. In the diagnosis of VUR, VCUG is still gold standard method. However, on which patients should VCUG be performed is still unclear, because of its several disadvantages including radiation exposure, the risk of secondary infection and patients' discomfort. Therefore, selective VCUG in children with UTI has been recommended to those with clinical risk factors such as younger age, recurrent UTI, or abnormal results of other noninvasive imaging studies. In the present study, we aim to assess the association of abnormalities detected on DMSA scan with the presence of VUR on VCUG in children with recurrent UTI.

It has been found that the sensitivity and specificity of DMSA scan for detecting VUR on VCUG was 89.13%(76.43-96.38%) and 44.44%(33.96-55.30%), respectively. The positive and negative predictive values and positive and negative likelihood ratios were, 45.05%(34.60-55.84%), 88.89% (75.95-96.29%), 1.60% (1.30-1.98%), 0.24 % (0.10-0.58%), respectively, in our study. In a previous study, including 50 children younger than ten years of age with recurrent UTI, the sensitivity, and specificity of DMSA scan for detecting VUR on VCUG were founded to be 95.45%, 35.71%, respectively (6). Tseng et al. studied 142 children younger than 2 years of age with first febrile UTI and reported sensitivity and specificity of 100%, 34%, respectively (12). Sensitivity was found to be 96% in a study involving 290 infants with first febrile UTI by Preda et al (13). Yet, Fouzas et al. reported a sensitivity of 69.6%, which is much lower than that reported by the present and abovementioned studies. Results of different studies were summarized in table 4 (14).

Table 4. Parameters of diagnostic performance of DMSA for detecting grade III-V VUR at VCUG, in different studies (6, 12, 13, 14, 15)

Parameters	Hansson et al. (2004)	Tseng et al. (2007)	Preda et al. (2007)	Fouzas et al. (2010)	Awais et al. (2014)	Present study
Sensitivity	80.55%	100%	96%	76.0%	95.45%	87.80%
Specificity	80.90%	34%	57.6%	63.5%	35.71%	42.11%
Positive predictive value	36.25%	21%	17%	16.1%	53.85%	39.56%
Negative predictive value	96.86%	100%	99%	96.6%	90.91%	88.89%
Positive likelihood ratio	4.21	1.51	2.06%	2.10	1.48	1.52
Negative likelihood ratio	0.24	0	0.07%	0.38	0.13	0.29

Nevertheless, it should also be considered that the number and the age of patients in these studies are not exactly equal to each other.

It has been founded in the present study that the sensitivity and specificity of both DMSA scan and renal USG for detecting VUR on VCUG was 78.05% (62.39-89.44%) and 44.44% (47.33-67.96%), respectively. The positive and negative predictive values and positive and negative likelihood ratios were, 44.44% (32.72-56.64%), 85.94 % (74.98-93.36%), 1.85(1.39-2.47), 0.38(0.21-0.69) in our study. Parameters of diagnostic performance of DMSA for detecting grade III-V VUR at VCUG, in different studies were presented in Table 4. As compared to other studies, the sensitivity of DMSA was found as 87.8%, while the specificity was 42.1% in our study.

The ratio of VUR at any grade and high-grade VUR were founded to be 34% and 31%, respectively in our study. In the study of Awais et al., which is similar to the present study, the ratio of high-grade VUR was established to be 44% (6).

The false positive-rate of DMSA scan for the detection of VUR reported in our study was 37.5%. It was reported to be respectively, 61.1%, 45%, 32.3%, in the studies of by Awais et al., Tseng et al. and Preda et al. (6,12,13).

The renal scar is an irreversible change of the kidney, even if the VUR resolves and a false - positive DMSA scan can result from this condition. We evaluated patients with recurrent UTI, and permanent renal damage was more likely in our patients even in the absence of VUR. Though we had a high false positive rate of DMSA scan, we prevented 63.5% of from undergoing VCUG and our study established a high negative predictive value and low negative likelihood ratio of 88.89% and 0.29 respectively.

In many recent studies has been recommended a DMSA scan as the initial investigation; VCUG is only indicated in the patients with abnormal DMSA findings, recurrent UTIs. To avoid unnecessary VCUG because of its disadvantages, we evaluated DMSA scan as a rule out test for high-grade VUR.

In conclusion, we had high sensitivity and negative predictive value for ruling out VUR on VCUG with recurrent UTI. We suggest that DMSA scan may be an initial investigation before VCUG in children with recurrent UTIs.

No conflict of interest.

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