



Abnormal DMSA renal scan findings and associated factors in older children with vesicoureteral reflux

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Abstract

Aim There are scanty data on the rate of abnormal Tc-99 m dimercaptosuccinic acid (DMSA) renal scintigraphy and associated factors in children older than 5 years with diagnosis of VUR. We do not have knowledge about which older children should undergo DMSA after VUR diagnosis. This study aims to assess the rate of abnormal DMSA findings and associated factors in children older than 5 years of age diagnosed with VUR.

Materials and methods We retrospectively reviewed the medical records of 258 children with VUR diagnosed at or older than 5 year age. 179 children [42 (23.5%) males and 137 (76.5%) females] with complete data were included. 268 reflux units were compared according to gender, bilaterality, grade, reflux phase at voiding cystourethrography, febrile urinary tract infection (fUTI), lower urinary tract dysfunction (LUTD), and DMSA findings with uni- and multivariate analysis.

Results The median age was 110 (60–216) months. VUR grades were I, II, and III in 197 (73.6%) units and IV–V in 71 (26.4%). 138 (51.5%) renal units had abnormal DMSA. VUR grade ($p < 0.01$), unilaterality ($p = 0.048$), and fUTI ($p = 0.031$) in univariate but only grade and unilaterality in multivariate analysis are significantly associated with abnormal DMSA. Although reflux at filling phase was predominant in high-grade VUR group, reflux at voiding phase ($p = 0.006$) in low–medium-grade (1–3) VUR was associated with abnormal DMSA.

Conclusion Children older than 5 years of age diagnosed with VUR should be regarded as a high-risk group for abnormal DMSA regardless of gender, unilaterality, grade, reflux phase, fUTI, and LUTD.

Keywords Vesicoureteral reflux · DMSA · Children · Renal scar · Urinary tract infection

Introduction

The most common congenital urologic disease in children with febrile urinary tract infections (fUTI) leading to renal impairment is vesicoureteral reflux (VUR) [1]. VUR has an

expanding body of literature on evaluation, screening, and management of the disease [2]. Evaluation and management recommendations for VUR are constructed depending on gender, age, VUR grade, abnormal Tc-99 m dimercaptosuccinic acid (DMSA) renal scan findings, frequency of fUTI,

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and lower urinary tract dysfunction (LUTD) in the American Urological Association (AUA), European Association of Urology (EAU)-European Society for Pediatric Urology (ESPU) guidelines [3, 4]. Briefly, invasive and radiohazard diagnostic modalities should be selected wisely to define the risk groups, and treatment options should be discussed to prevent new renal scarring for the best personalized care.

Studies reported that low-grade VUR, voiding phase reflux at VCUG, younger age, infrequent fUTI, absence of LUTD, and normal DMSA renal scan could predict higher rates of spontaneous resolution until 5 years of age [5–8]. Moreover, reports on higher rate of normal DMSA findings in low-grade VUR may make DMSA renal scan avoidable in some children [9]. However, inconsistent reports on rates of DMSA abnormality in VUR ranging from 6–10% [10, 11] to 30–60% [12–15] have been published. Interestingly, there is not enough information in which older children with VUR we can avoid DMSA renal scan. Noticeably, all guideline recommendations are principally based on prospective studies on children diagnosed and followed from small ages. We do not know how valid those recommendations are in older children whose spontaneous resolution is more unlikely.

In this study, we aimed to evaluate the rate of abnormal DMSA renal scintigraphy in children diagnosed with VUR at or over 5 years of age and association of characteristics such as gender, VUR grade, bilaterality, reflux phase at VCUG, fUTI, and LUTD with abnormal DMSA renal scan.

Materials and methods

We reviewed 258 children diagnosed with VUR at and older than 5 years of age from June 2014 and December 2019 in our clinic. The approval of the local ethics committee was obtained (Ethical Number: 09.2020.1175). Informed consent was obtained from parents before the study. In total, 79 children were excluded due to missing data, other associated urinary abnormalities leading to secondary VUR such as ureterocele, duplicated or ectopic ureter, bladder abnormality, neurogenic LUTD, posterior urethral valve, urethral stricture, and urinary stone surgery. A total of 179 children who had complete cyclic VCUG and DMSA renal scintigraphy data were included in the study. In all cases, VCUG was first performed due to fUTI and/or hydroureteronephrosis. The Society of Fetal Urology (SFU) grading system was used to evaluate hydronephrosis. DMSA renal scintigraphy was performed at least 3 months after fUTI in every VCUG confirmed VUR case. Each VUR was recorded as a refluxing unit in VUR grades by International Reflux Study Classification System [16]. Abnormal DMSA renal scan was accepted as at least one cortical uptake defect on the affected kidney or the differential function of the kidney less than 40% [17].

VCUG was performed under the guidance of the standard protocol of the American Academy of Pediatrics [18]. Voiding was requested before VCUG in toilet-trained children. Then, 6 or 8 Fr non-balloon catheter was inserted into the urethra and residual urine volume was drained. The bladder was filled at a rate of 10% of expected bladder capacity per minute with radiographic contrast at body temperature. During filling and voiding, multiple spot images in anterior–posterior, right and left oblique were obtained. Reflux phases were recorded as filling and voiding reflux during VCUG. After urethral catheter placement, the time period that began from the entry of contrast material and last entry of the material into the bladder was defined as the filling reflux. Reflux during the voiding after the appearance of the contrast material within the proximal urethra until the completion of the study was defined as the voiding reflux.

All children underwent questioning on storage and voiding complaints with Dysfunctional Voiding and Incontinence Scoring System [19], voiding diary for 48 h, and uroflowmetry with residual urine measurement. Normal lower urinary tract functions were considered as no urgency, no daytime wetting, 3–8 times daytime urination with bladder volume compatible with estimated bladder capacity according to age (EBC), and normal flow curve with normal residual volume [20]. The EBC was calculated with a formula: $(\text{age} + 2) \times 30$ [21]. Gender, bilaterality, VUR grade, reflux phase at VCUG, fUTI at presentation, LUTD, and findings in DMSA renal scintigraphy were recorded.

Statistical analysis

Categorical data were presented with counts and percentages. Normality assumption of the continuous data was verified with the Shapiro–Wilk test and data did not show normal distribution. Continuous data were presented with means and interquartile range (IQR). Chi-square test was used to compare categorical variables. Mann–Whitney *U* test was used to compare continuous variables. For all tests, a *p* value less than 0.05 was considered to indicate statistical significance. Associated factors were evaluated with logistic regression analyses. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The median age of 179 children (268 reflux units) was 110 (60–216) months. 42 children (23.5%) were male and 137 (76.5%) female. VUR grade was I, II, and III in 197 (73.6%) units and IV–V in 71 (26.4%) units (Table 1). VUR was present unilateral in 90 (50.3%) children and bilateral in 89 (49.7%). In a total of 268 reflux units, 195 (72.8%) units

Table 1 Gender, laterality, VUR grade, phase VUR at VCUG, fUTI at presentation, LUTD according to abnormal DMSA renal scan, and multivariable regression analysis for association of abnormal DMSA renal scan in units

	Normal DMSA <i>n</i> (%) <i>n</i> = 130 (48.5%)	Abnormal DMSA <i>n</i> (%) <i>n</i> = 138 (51.5%)	<i>p</i> value (U)	<i>p</i> value (M)	OR (95% CI)
Gender					
Boy	34 (52.3)	31 (47.7)	0.481		
Girl	96 (47.3)	107 (52.7)			
VUR grade					
1	42 (73.7)	15 (26.3)	<0.001		Reference
2	25 (41.0)	36 (59.0)		0.000	5.18 (2.25–11.92)
3	40 (50.6)	39 (49.4)		0.001	3.77 (1.68–8.47)
4	16 (42.1)	22 (57.9)		0.000	6.66 (2.52–17.6)
5	7 (21.2)	26 (78.8)		0.000	18.39 (5.83–58.02)
VUR phase					
Filling	97 (49.7)	98 (50.3)	0.508		
Voiding	33 (45.2)	40 (54.8)			
Bilateral VUR					
No	36 (40.0)	54 (60.0)	0.048	0.027	1.89 (1.07–3.33)
Yes	94 (52.8)	84 (47.2)			Reference
fUTI					
No	53 (57.6)	39 (42.4)	0.031		Reference
Yes	77 (43.8)	99 (56.3)		0.203	1.46 (0.82–2.59)
LUTD					
No	77 (52.4)	70 (47.6)	0.162		
Yes	63 (48%)	68 (52%)			

Chi-square test were used for statistical analysis

VUR vesicoureteral reflux, fUTI febrile urinary tract infection, LUTD lower urinary tract dysfunction, U univariate, M multivariate, OR odds ratio, CI confidence interval

were refluxing at filling and 73 (27.2%) refluxing at voiding phase. There were only 10 children concurrently with filling on one side and voiding reflux on the other. 138 renal units (51.5%) had abnormal DMSA. 58 (42%) renal units had single renal cortical defect and 80 (58%) had multiple. 176 (65.6%) renal units (118 (65.9%) children) had fUTI at presentation. 82 (45.8%) children had LUTD (65 overactive bladders, 17 dysfunctional voiders). 154 (86%) children were started on antibiotic prophylaxis and 72 (40.2%) on anticholinergics. All boys were circumcised.

Table 1 shows univariate and multivariate analysis of all parameters for abnormal DMSA in all units. In univariate analysis, VUR grade ($p < 0.01$), unilaterality ($p = 0.048$), and fUTI ($p = 0.031$) are found to be significantly associated with abnormal DMSA (Table 1). Multivariate analysis showed only VUR grade and unilaterality as the significant factors.

In Table 2, children with low–medium-grade reflux (Grade I–III) were compared according to abnormal DMSA. In univariate analysis, abnormal DMSA rate was significantly higher in voiding reflux compared to filling phase (52% vs 38%, $p = 0.037$) but not affected by unilaterality, fUTI at presentation, and LUTD. In the multivariate analysis, voiding reflux was the only significant parameter associated with abnormal findings on DMSA ($p = 0.006$).

In Table 3, children with high-grade reflux (Grade IV–V) were compared according to abnormal DMSA. Although fUTI, unilaterality, and LUTD was significant factors for abnormal DMSA finding in univariate analysis, only unilaterality ($p = 0.024$) was found to be significant in multivariate analysis. Abnormal DMSA scan had 67.6% sensitivity, 54.3% specificity, 34.8% positive predictive value, and 82.3% negative predictive value for predicting high-grade VUR [Odds Ratio 2.481 (1.402–4.390)].

Discussion

Herein, we aimed to study the rate of abnormal DMSA renal scan and associated factors in a specific group of children diagnosed with VUR at or older than 5 years of age. Since most studies on VUR are composed of children prospectively followed from infancy, evaluation and management recommendations for older children (over 5 years of age) are vague for timing for DMSA renal scan and management options. Literature is lacking in studies focusing on children first diagnosed with VUR at older ages. Therefore, we believe that this cross-sectional study of a specific group of children diagnosed with VUR at an older age with fUTI and/

Table 2 Gender, laterality, VUR grade, phase VUR at VCUG, fUTI at presentation, LUTD according to abnormal DMSA renal scan, and multivariable regression analysis for association of abnormal DMSA renal scan in units with low–medium-grade VUR (Grade 1–3)

	Normal DMSA n, (%) n=107 (54.3%)	Abnormal DMSA n, (%) n=90 (45.7%)	p value (U)	p value (M)	OR (95% CI)
Gender					
Boy	22 (57.9)	16 (42.1)	0.622		
Girl	85 (53.5)	74 (46.5)			
VUR phase					
Filling	77 (59.7)	52 (40.3)	0.037		Reference
Voiding	30 (44.1)	38 (55.9)		0.006	2.65 (1.32–5.3)
Bilateral VUR					
No	34 (46.6)	39 (53.4)	0.094		
Yes	73 (58.9)	51 (41.1)			
fUTI					
No	42 (59.2)	29 (40.8)	0.306		
Yes	65 (51.6)	61 (48.4)			
LUTD					
No	62 (54.9)	51 (45.1)	0.857		
Yes	45 (53.6)	39 (46.4)			

Chi-square test were used for statistical analysis

VUR vesicoureteral reflux, fUTI febrile urinary tract infection, LUTD lower urinary tract dysfunction, U univariate, M multivariate, OR odds ratio, CI confidence interval

or hydroureteronephrosis is important to define possible factors association with abnormal DMSA renal scan.

As seen in Table 1, we found 51.5% as rate of abnormal DMSA in all group which is very high compared to 10% of RIVUR trial. Abnormal DMSA rates in this specific older age group are very high even in low–medium grades (Grade 1 (26.3%), Grade 2 (59%), Grade 3 (49.4%), Grade 4 (57.9%), and Grade V (78.8%)). Clearly, the most important factor for abnormal DMSA in our study group is the VUR grade. Of course, we can anticipate such high rates of abnormal DMSA findings due to past fUTIs with VUR in the first 5 years of life. In the literature, older children scar rates are similar. Abnormal DMSA was reported in 83.9% (7 with a single scar, 7 with multiple lesions, and 12 with reduced kidney function) of children (mean age 7.6 years) with late diagnosis of VUR (only grade 3–5) [22]. However, it is interesting to note that abnormal DMSA rates in Grade 2–3–4 are very similar (49.4–59%) where Grade 1 (26.3%) and Grade 5 (78.8%) deviate significantly. We can speculate that either a downgrading from high to low grades occur even after renal scarring occurs or renal scarring risk is similar in Grade 2–4. Heterogeneity of mid- and long-term results depending only

Table 3 Gender, laterality, VUR grade, phase VUR at VCUG, fUTI at presentation, LUTD according to abnormal DMSA renal scan, and multivariable regression analysis for association of abnormal DMSA renal scan in units with high-grade VUR (Grade 4–5)

	Normal DMSA n, (%) n=23 (32.8%)	Abnormal DMSA n, (%) n=48 (67.2%)	p value (U)	p value (M)	OR (95% CI)
Gender					
Boy	12 (44.4)	15 (55.6)	0.089		
Girl	11 (25)	33 (75)			
VUR phase					
Filling	20 (30.3)	46 (69.7)	0.171		
Voiding	3 (60)	2 (40)			
Bilateral VUR					
No	2 (11.8)	15 (88.2)	0.037	0.024	8.47 (1.33–54.01)
Yes	21 (38.9)	33 (61.1)			Reference
fUTI					
No	11 (52.4)	10 (47.6)	0.020		Reference
Yes	12 (24)	38 (76)		0.052	4.03 (0.99–16.45)
LUTD					
No	15 (44.1)	19 (55.9)	0.043		Reference
Yes	8 (21.6)	29 (78.4)		0.867	1.12 (0.29–4.41)

Chi-square test were used for statistical analysis

VUR vesicoureteral reflux, fUTI febrile urinary tract infection, LUTD lower urinary tract dysfunction, U univariate, M multivariate, OR odds ratio, CI confidence interval

on VUR grades show that more factors could be associated with abnormal DMSA even under treatment. In the RIVUR trial, both the rate of abnormal DMSA in Grade I, II, III, and Grade IV were 7.6%, 4.7%, 10%, and 35.2%, respectively. The rates of new scar development at the end of the study (2 years) were similar in the prophylaxis (6%) and placebo (7%) arms [11]. However, our group is very different from RIVUR trial in terms of patient age and rate of abnormal DMSA. In this older age group, even grade I VUR have over 25% risk of having an abnormal DMSA. In our practice, we continue to advocate DMSA renal scan in older children with any grade of VUR.

We found that reflux grade ($p < 0.001$) and unilateral reflux ($p = 0.048$) are significant factors for abnormal DMSA in all group in multivariate analysis (Table 1). There may be more factors other than VUR grade such as gender, frequent fUTI, LUTD, and, recently, bladder volumes and reflux phases in VCUG associated with abnormal DMSA. In our study, it is noteworthy to find no association of reflux phase with abnormal DMSA. However, we noted filling reflux (92.9%) was profoundly predominant in

high-grade (IV–V) VUR, whereas 65.4% in low–medium (I–III) grades. Then, we divided children into low–medium (I–III) and high grades (IV–V) to obtain more homogeneous groups. As pointed out in Table 2, we found that voiding reflux was strongly associated with abnormal DMSA renal scan only in low–medium VUR grades ($p=0.006$) in the multivariate analysis.

Our findings regarding reflux phase distribution in children with all VUR grades are similar to studies focusing on reflux phases (filling vs. voiding, 72.7% vs 27.3%) [6, 23]. However, interestingly, filling reflux (92.9%) was very highly predominant in high-grade VUR (abnormal DMSA with 67.6%) as seen in Table 3. The rate of filling reflux was 74.2% in the study of Lee JN et al. [6], and 66.2% in Han DS et al. [23]. Moreover, discrepancy in rates of voiding reflux in low–medium (33.7%) and high VUR grades (9.1%) was also noted by another study [23]. Spontaneous reflux resolution and endoscopic surgical success rates are also claimed to increase in voiding reflux [5, 6, 23]. Filling reflux with small bladder capacity in young children was also reported to be a predictor for breakthrough fUTI in a univariate analysis [24]. However, we observed that filling reflux (92.9%) is a typical characteristic of high-grade VUR (IV–V) and high-grade VUR is already associated with higher abnormal DMSA rate (67.6%) (Table 3). Therefore, on the contrary of the report by Alexander et al. [24], we found that that voiding reflux is significantly associated with abnormal DMSA only in low–medium VUR grades ($p=0.006$). We believe that reflux phase is an uncountable entity changing with VUR grade, and hence, DMSA renal scan should be performed in older children regardless of reflux phase.

Although LUTD has been reported as a factor for frequent fUTI and low spontaneous resolution, we could not show an association between LUTD and abnormal DMSA in all VUR grades ($p=0.719$) in our group (Table 1). Lee et al. retrospectively studied 94 children with 136 renal units with a mean age of 54.26 ± 37.31 months [6]. Majority of their study group consisted of high-grade VUR (63.9%) and filling reflux (74.3%). Authors could not show a correlation of LUTD with endoscopic treatment success and reflux phase. Moreover, we noted that gender has no association in abnormal DMSA in low–medium VUR grades (Table 2) and high VUR grades (Table 3). This could be a reflection of higher resolution rate in males with high-grade reflux in younger ages [25] and older females are more prone to frequent fUTI [15]. We believe that our older age group is valuable to test the association of gender and LUTD to abnormal DMSA, since LUTD evaluation can be more accurately performed and long-term results in gender could be better comprehended. We believe that DMSA renal scan should be performed in older children regardless of gender and LUTD presence.

Another interesting finding in our study is that unilateral VUR is an independent risk factor for abnormal DMSA in VUR patients (Table 1, $p=0.027$). We found that this association is more significant in high-grade VUR (Table 3, $p=0.024$, OR (95% CI)=8.47 (1.33–54.01)). However, this finding can be due to congenital dysplastic kidney. It has been suggested that unilaterality is not associated with renal scarring [11]. We believe that DMSA renal scan should be performed regardless of uni or bilaterality of VUR in older children.

Another point in the current study is the unclear impact of fUTI in abnormal DMSA. We took into account fUTI only as the presentation symptom of children, since past fUTI history is unreliable due to missing medical records. There are solid data that scarring occurs due to fUTI as the rationale of renal scarring pathophysiology [11, 15]. Older age group may be regarded different than younger age in terms of fUTI and scarring association where the renal scarring occurs mostly in first 2 years of age [15]. Moreover, one of the predisposing factors for breakthrough fUTI is frequent fUTI before VUR diagnosis [26, 27]. In our group, 65.6% of renal units presented with fUTI (Table 1) and this rate was 70.4% in high-grade VUR (Table 2) and 63.9% in low–medium VUR (Table 3). We can conclude that fUTI continue in the majority, but, as seen in multivariate analysis in Tables 2 and 3, it is probably not an independent factor for low–medium and high VUR grades ($p=0.4$, $p=0.052$) at older age group, since scarring has already occurred. We strongly believe that lack of fUTI at presentation should not prevent DMSA renal scan in older children.

Our study suffers from being a cross-sectional study of medical records in a specific group. Unfortunately, we do not have the data of the incidence of dysplastic renal abnormalities and fUTI-associated scarrings. Moreover, we have no proof for downgrading of high-grade VUR to low–medium in the first 5 years of age. Also, we have no insight about the possible changes in reflux phases and LUTD as the bladder enlarges and voiding matures with age. We did not compare the abnormal DMSA findings with grade of hydronephrosis, renal cortical thickness, and anterior–posterior diameter of renal pelvis. Follow-up of patients with normal DMSA renal scans and high-grade VUR were not evaluated because of the cross-sectional nature of the study. Other limitations of the study are the relatively small number of patients and the absence of follow-up data. However, this study points out that older age children with late diagnosed VUR should be regarded as a high-risk group due to high rates of abnormal DMSA findings.

Conclusion

We, herein, report that children older than 5 years of age diagnosed with VUR suffer from abnormal findings on DMSA in over half of cases. Children older than 5 years of

age should be regarded as a high-risk group for abnormal DMSA renal scan findings regardless of gender, bilaterality, grade, reflux phase at VCUG, FUTI at presentation, and LUTD.

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Declarations

Conflict of interest No conflict of interest was declared by the authors.

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