Relationship Between Vesicoureteral Reflux and Renal Scarring in Children with Urinary Tract Infection

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ABSTRACT

Objective: To evaluate the association of vesicoureteral reflux (VUR) in comparison with the development of renal scarring in child patients with urinary tract infection (UTI).

Methods: This study involved a retrospective review. Patients under 14 years old with a diagnosis of UTI with a positive urine culture and who had a voiding cystourethrogram (VCUG) and technetium 99 m dimercaptosuccinic acid (Tc-99m_DMSA) renal scintigraphy performed within 4-6 months after acute UTI were included in the study. The VCUG results were classified as positive or negative for vesicoureteral reflux (VUR). If reflux was present, the severity was graded according to the recommendation of the International Reflux Study in children.[1] The Tc-99m DMSA results were interpreted as positive or negative for renal scarring. Statistical analysis was performed using the $\chi 2$ test or Fisher's exact test and Mann–Whitney test to compare the presence of VUR and renal scarring as well as the grading of the VUR and renal scarring. Positive and negative likelihood ratios (LR) were calculated.

Results: In total, 185 patients (74 girls and 111 boys; mean age, 3.5 years old) were included in the study. There were five children with only a single kidney, resulting in 365 kidneys for analysis. Vesicoureteral reflux was found in 203 (55.6%) kidneys, classified as grades 1, 2, 3, 4, and 5 in 19, 31, 81, 38, and 34 kidneys, respectively. Scarring was found in 110 of 203 kidneys (54.2%) with VUR and in 18 of 162 kidneys (11.1%) without VUR ($p < 0.0001$). The LR positive was 2.2 (95%CI, 1.9-2.5) and LR negative was 0.23 (95% CI, 0.1-0.4).

Conclusion: There was a significant correlation between positive VUR and the development of renal scarring. Patients with positive VUR should be considered for a Tc99m-DMSA scan to evaluate them for the development of renal scarring.

Keywords: Vesicoureteral reflux; VUR; renal scar; urinary tract infection; UTI (Siriraj Med J 2021; 73: 26-31)

INTRODUCTION

Urinary tract infection (UTI) is a common cause of acute illness in infants and children. The infection may involve the upper part of the urinary tract (kidneys and ureters) or the lower urinary tract (bladder and urethra). Patients with renal infection or pyelonephritis may develop renal scarring, hypertension, and end-stage renal dysfunction later in life. It is mandatory to identify these patients with acute pyelonephritis to prevent further renal damage. Clinically, urinary tract infection with the presence of fever increases the probability of renal involvement. Moreover, there is an increased risk of underlying urologic abnormalities as well as a greater risk of consequent renal scarring.[2]

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Renal scarring is considered a cause of long-term morbidity. The prevalence has been reported to be about 10-40%.[3] Young age, delayed treatment, the presence of vesicoureteral reflux (VUR), and recurrent episodes of pyelonephritis are associated with an increased risk of renal damage.

In children with UTI, the most important reason for performing an investigation is to identify abnormalities of the genitourinary tract that may require additional evaluation and management.

Renal and bladder ultrasonography is a noninvasive procedure and is always the first line of investigation. The size and shape of the kidneys, dilatation of the ureters, and the presence of gross anatomic abnormalities can be demonstrated with this technique. However, it is not reliable in diagnosing renal scarring.[4]

Technetium-99m dimercaptosuccinic acid (Tc-99m DMSA) renal scintigraphy can be used to detect acute pyelonephritis and renal scarring in acute and chronic settings. However, using DMSA as the initial test is more expensive and involves radiation exposure. According to the American Academy of Pediatrics guidance, DMSA is not recommended as a routine evaluation for children with a first UTI.[5]

Voiding cystourethrogram (VCUG) is the study of choice to establish the presence and degree of vesicoureteral reflux (VUR). A prior study reported an approximately 25% to 30% incidence of VUR in children (0 to 18 years old) with a first UTI.[6] Even though VUR is a significant risk factor for the development of renal scarring, the exact relationship between VUR and scarring is still undetermined.[7] Therefore, VCUG cannot directly diagnosis renal scarring.

The purpose of this study was to determine if the presence and severity of VUR can predict the development of renal scarring in children with febrile UTI.

MATERIALS AND METHODS

The study was approved by the Institutional Ethics Committee of Siriraj Hospital (Si 283/2019). This study was a retrospective single-center study. Medical records were searched using the keywords "febrile UTI" in patients less than 14 years old from January 2016 to July 2018. Only patients with a positive urine culture and who had both VCUG and a DMSA scan done within 4-6 months of each other were included in this study.

Demographic data and blood urea nitrogen (BUN) as well as creatinine result were recorded. The VCUG results were reviewed by a pediatric radiologist and a radiology resident who were unaware of the patients' test results. The results were classified as positive or negative for VUR. The degree of vesicoureteral reflux was graded according to the recommendations of the International Reflux study in children[1]:

Grade 1: Reflux into a non-dilated ureter.

Grade 2: Reflux into the upper collecting system but non-dilated.

Grade 3: Mild or moderate dilatation and/or tortuosity of the ureter and mild or moderate dilatation of the renal pelvis.

Grade 4: Moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the renal pelvis and calyces.

Grade 5: Gross dilatation and tortuosity of the ureter. Gross dilatation of the renal pelvis and calyces and the loss of papillary impressions.

Dimercaptosuccinic acid renal scintigraphy was performed using a standard procedure. The patients were injected with DMSA 0.1 mCi/kg (minimum dosage of 0.3 mCi and maximum dosage of 3 mCi). Data were acquired on a dual-head, large field of view, gamma camera equipped with a low-energy high-resolution collimator in 256 × 256 matrices.

Relative tracer uptake (RU) was calculated as the mean value of uptake in the anterior and posterior projections, corrected for background activity. The presence of focal defects in the renal cortex with distortion or indentation of the normal renal outline, renal volume loss, and cortical thinning were classified as renal scarring. If the result was undetermined, DMSA was repeated in the next six months, and the final result was used for interpretation.

Statistical analysis

The Mann–Whitney test and chi-square test were used for statistical analysis between the groups of children with VUR and without VUR, and between the different grades of VUR, considering a *p*-value of less than 0.01 as statistically significant.

Positive and negative likelihood ratios (LR) along with 95% confidence intervals (CI) were calculated for VCUG using DMSA as the gold standard for permanent renal damage.

RESULTS

Overall, there were 598 children aged 0-14 years old with febrile UTI. Of those, 185 children (74 girls and 111 boys; mean age, 3.5 years old) met all the criteria with a positive urine culture and had had both diagnostic studies performed (Table 1). There were five children with only a single kidney each, resulting in 365 kidneys for analysis.

Vesicoureteral reflux was found in 203 kidneys (55.6%). Refluxes were classified as grades 1, 2, 3, 4, and 5 in 19, 31, 81, 38, and 34 kidneys, respectively

DMSA scintigraphy showed normal renal uptake in 237 kidneys (65%) and renal scarring in 128 kidneys (35%). In 6 kidneys, the result was equivocal in the first study, but subsequently demonstrated renal scarring on the following examination.

Scarring was shown in 110 of 203 (54.2%) kidneys with VUR and in 18 of 162 (11.1%) kidneys without VUR (Table 2). The incidence of DMSA renal scarring was significantly associated with the presence of a refluxing kidney ($p < 0.001$). The sensitivity of VCUG in the prediction of renal scarring was 85.94% (95% CI, 78.7-91.4), and the specificity was 60.76% (95%CI, 54.2-67.0).

The number of kidneys with renal scarring compared with the different grades of VUR was calculated (Table 3). The positive and negative likelihood ratios (LR) of VUR in detecting renal scarring was calculated according to VUR grading. The cumulative data for the presence of VUR from grades 1-5 caused a positive LR of 2.2 (95% CI, 1.9-2.5), and a negative LR negative of 0.23, (95%, CI 0.1-0.4) (Table 4).

One hundred and sixty-six patients had BUN and creatinine in medical records. Five in 166 patients (9 in 365 kidneys) had high creatinine levels indicating impaired renal function. Four kidneys in these patients were associated with vesicoureteral reflux, grade 2 in 1 kidney, grade 3 in 1 kidney and grade 4 in two kidneys. There were 5 kidneys in patients with abnormal renal function that were not associated with vesicoureteral reflux.

TABLE 1. Demographic data of the study patients with UTI.

Age (year)	Sex		Total
	Male	Female	
0-5	88	55	143 (77.3%)
>5-10	20	14	34 (18.4%)
>10-15	3	5	8 (4.3%)
Total	111	74	185 (100%)

TABLE 2. Comparison of the VUR results with renal scarring.

	Scar	No scar	Total
VUR	110	93	203
Non-VUR	18	144	162
Total	128	237	365

Sensitivity 85.9% (95% CI: 78.7-91.4), Specificity 60.8% (95%CI 54.2-67.0)

TABLE 3. Comparison of the kidneys with negative and positive VUR in different grades for testing for renal scarring.

VUR	Scar	No scar	Total kidneys	% of kidneys with a scar
No VUR	18	144	162	11.1
Grade 1	9	10	19	47.4
Grade 2	12	19	31	38.7
Grade 3	45	36	81	55.6
Grade 4	21	17	38	55.3
Grade 5	23	11	34	67.6
Total	128	237	365	

TABLE 4. Likelihood ratio (LR) for renal scarring in different grades from VUR.

	+LR	-LR
Grade 1-5	2.2 (95%CI 1.9-2.5)	0.2 (95%CI 0.1-0.4)
Grade 2-5	2.3 (95%CI 2.0-2.6)	0.3 (95%CI 0.2-0.5)
Grade 3-5	2.6 (95%CI 2.2-3.0)	0.4 (95%CI 0.3-0.6)
Grade 4-5	2.9 (95%CI 2.3-3.7)	0.7 (95%CI 0.5-1.1)
Grade 5	3.9 (95%CI 2.7-5.6)	0.9 (95%CI 0.5-1.5)

DISCUSSION

Urinary tract infection is one of the most common causes of bacterial infections in childhood. The diagnosis and management of UTI continue to be controversial with many challenges in clinical practice.

In terms of imaging investigations in patients with UTI, there is no consensus on a single guideline in the pediatric population. The method and timing of imaging to evaluate for urinary tract anatomical abnormalities and renal scarring after a febrile UTI vary between institutions.

Technetium-99m DMSA seems to be the most reliable method for the diagnosis of chronic cortical renal scarring. Prior studies suggested that DMSA may obviate VCUG in the evaluation of febrile UTI. [8,9] However, this method requires nuclear medicine specialists and may not be available in all institutions. VUCG is an optimal method to diagnose VUR as well as for assessing the degree of VUR and the anatomy of the male urethra. However, VCUG cannot detect renal scarring or pyelonephritis.

In our study, we wanted to assess if the presence and severity of VUR could predict the development of renal scarring in children with UTI. We found that the incidence of DMSA renal scarring was significantly associated with the presence of vesicoureteral reflux. Renal scars were found in 54.2% of kidneys with VUR and 11.1% of kidneys with no VUR.

Our study findings concurred with prior research. For instance, Canoe et al. found renal damage in 67% of kidneys with VUR and in 16% of kidneys with no VUR, and concluded that the presence of VUR was associated with renal damage.[10]

However, some prior studies do not concur with our results.[11,12] For instance, Moorthy et al. found that only 16% of children with VUR had an abnormal kidney on

DMSA scan. The heterogeneity of the published results may depend on several factors, such as the ages and types of patients, the timing between UTI and investigation, and the antibiotic treatments applied.

Our study also compared the incidence of renal scarring with the VUR results according to the severity of VUR using VUR grading. We found that there was a slight increase in the percentages of the kidneys with renal scars as the grade of the VUR increased; from 47.4% with VUR grade 1 to 67.6% in VUR grade 5. However, from our results, the percentage of renal scarring in grade 2 reflux was less than in grade 1.

Prior studies also reported VUR as a risk factor for developing a renal scar and increased renal scarring in patients with a higher grading of VUR.[13,14] Other risk factors of renal scarring included recurrent UTI, bladder-bowel dysfunction, and delayed treatment.[15]

Interestingly, we also observed BUN and creatinine levels in comparison with VUR and scarring. We found that most patients (161 of 166) had normal BUN and creatinine levels. There were 5 patients with 9 kidneys with impaired renal function. In these patients, less than 50% of kidneys had reflux on VCUG in different grades from 2 to 4. We suggested that there was no direct correlation between VUR and renal function, which can be explained by the fact that patients have two kidneys. Severe VUR or scarring in one kidney will not lead to abnormal renal function with high BUN and creatine levels. It could be different if the patient had a single kidney. In fact, we had one patient with a single kidney with VUR grade4 and had renal failure.

To evaluate the significance of VUR, we also looked at the likelihood ratio with the different VUR grades. We found that the positive likelihood ratio was slightly increased if we included only higher grades of VUR. However, the ranges of positive LR were between 2.2 and 3.9. A low number positive LR presumes that VCUG may not be a useful diagnostic test to detect renal scarring. From our study, 11.1% of scarred kidneys would have been missed if Tc-99m DMSA was not performed in patients with no VUR and 14.9% would have been missed if we had avoided Tc-99m DMSA in patients with no VUR and VUR grade 1 (Figs 1 A, B, and C).

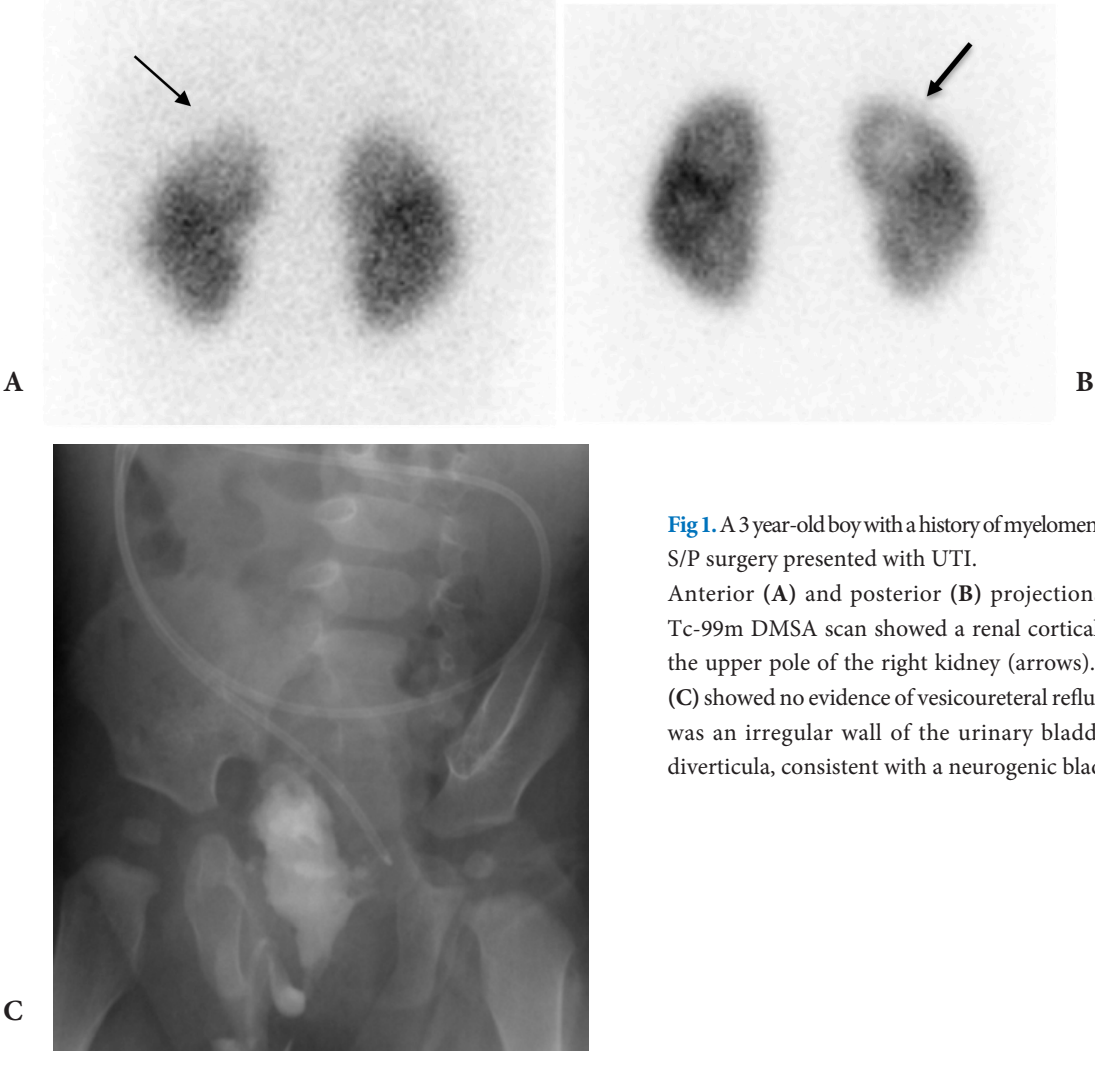

Fig 1. A 3 year-old boy with a history of myelomeningocele S/P surgery presented with UTI.
Anterior **(A)** and posterior **(B)** projections of the Tc-99m DMSA scan showed a renal cortical scar at the upper pole of the right kidney (arrows). VCUG **(C)** showed no evidence of vesicoureteral reflux. There was an irregular wall of the urinary bladder with diverticula, consistent with a neurogenic bladder.

Our study has several limitations. First, this was a retrospective study. There was a diversity of patients in terms of VCUG techniques. Some patients might have a cyclic filling of the contrast medium. The different kinds and durations of the antibiotic treatments might also have affected the results. A large prospective result would be useful for the homogeneity of the population.

CONCLUSION

From our study, we found that there was a significant correlation between positive VUR and the development of renal scarring. The number of scarred kidneys also slightly increased as the grade of VUR increased. Moreover, the presence of low-grade VUR cannot exclude renal scarring and these cases should be considered for further evaluation and a follow up with Tc99m- DMSA.

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