Accuracy of Early DMSA Scan for VUR in Young Children With Febrile UTI

WHAT’S KNOWN ON THIS SUBJECT: The sensitivities of 99mTc-dimercaptosuccinic acid in predicting vesicoureteral reflux reported by different institutions were at different levels for young children with acute febrile urinary tract infection.

WHAT THIS STUDY ADDS: An acute 99mTc-dimercaptosuccinic acid scan is of great value in predicting dilating vesicoureteral reflux in children ≤2 years of age with a febrile urinary tract infection.

Abstract

OBJECTIVE: To evaluate the accuracy of an acute 99mTc-dimercaptosuccinic acid (DMSA) scan in predicting dilating vesicoureteral reflux (VUR) among young children with a febrile urinary tract infection (UTI).

METHODS: The medical records of children (≤2 years of age), presenting with febrile UTI between January 2000 and December 2011, were retrospectively reviewed.

RESULTS: A total of 523 children were included in this study, of whom 397 children (75.9%) had abnormal DMSA results and 178 children (34.0%) were identified as VUR on micturating cystourethrography (MCU). Among all the patients, the number of children with dilating VUR was 151 (28.9%). The rate of abnormal results on DMSA for the dilating VUR group was significantly higher than the rates for the non-VUR and low-grade VUR groups (P < .01). In the ≤6 months age group and ≥6 months age group, the sensitivities of DMSA in predicting dilating VUR were 96.15% and 100.0%, respectively, the negative predictive values were 97.26% and 100.0%, respectively, and the negative likelihood ratios were 0.0911 and 0.0000, respectively.

CONCLUSION: For children ≤2 years of age with a febrile UTI, an acute DMSA scan is valuable in the exclusion of dilating VUR. The likelihood of the presence of dilating VUR on MCU is rather low when the result of DMSA is negative. DMSA should be conducted to assess the need for an MCU. Pediatrics 2014;133:e30–e38

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Key Words: DMSA, UTI, VUR, MCU

Abbreviations
CI—confidence interval
DMSA—99mTc-dimercaptosuccinic acid
LR—likelihood ratio
MCU—micturating cystourethrography
UTI—urinary tract infection
VUR—vesicoureteral reflux

Dr Zhang collected the data, conceptualized and designed the study, and drafted the initial manuscript; Dr Xu conceptualized and designed the study and critically reviewed the manuscript; Dr Shen carried out the analyses and reviewed and revised the manuscript; Drs Cao and Zhai coordinated the data collection and reviewed and revised the manuscript; Drs Rao, Sun, Fang, Guo, Zhou, Bi, Zhao, and Pa coordinated the data collection; and all authors approved the final manuscript as submitted.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2014 by the American Academy of Pediatrics

Financial Disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose.

Funding: Supported by the Ministry of Chinese Science and Technology (2011CB944001).

Potential Conflict of Interest: The authors have indicated they have no potential conflicts of interest to disclose.
Urinary tract infection (UTI) is a common pediatric infectious disease, which affects up to 6% of girls and 1% of boys during childhood. It is of note that it may cause damage to the kidneys, such as renal scarring, especially when combined with urinary tract malformations. Therefore, guidelines of pediatric UTI evaluation were made to place emphasis on the imaging examinations for early diagnosis of renal lesions and urinary tract malformations in many countries.

Micturating cystourethrography (MCU) and 99mTc-dimercaptosuccinic acid (DMSA) scanning are 2 imaging methods being used at present. Although it is the gold standard technique for diagnosing vesicoureteral reflux (VUR), MCU also has shortcomings: invasiveness, extensive exposure of patients to radiation, and increased risk of reinfection. DMSA was recently proposed to predict the existence of VUR. However, for young children with acute febrile UTI, the sensitivities of DMSA in predicting VUR were reported at different levels by different institutions. Controversy still exists regarding whether a normal DMSA scan result could obviate MCU. To evaluate the accuracy of an acute DMSA scan in predicting dilating VUR, we retrospectively reviewed the medical records of children (≤2 years of age) with febrile UTI between January 2000 and December 2011.

METHODS

Subjects

This was a retrospective, single-center study. The potential subjects were ≤2-year-old patients who came to our tertiary pediatric hospital for the first time between January 2000 and December 2011 and were diagnosed with febrile UTI because of the following conditions: rectal temperature ≥38°C, either more than 5 white blood cells in urinalysis and more than a 10³ colony count of 1 microorganism in urine culture or by demonstration of acute pyelonephritis with DMSA scanning in patients with negative culture results who had received antibiotics before a urine culture was performed. For most patients, the urine specimens were from a clean voided midstream collection. For younger infants whose midstream urine specimens were difficult to collect, their specimens were collected by catheterization. Cystoscopic examination is not a routine procedure for boys in our country. All of the boys were circumcised. It was unclear whether this was the first UTI for these patients, but it was certain that this was the first time they had ever had imaging investigations of the urinary tract.

The exclusion criteria were (1) patients with other urogenital or anorectal malformations and (2) patients who failed to complete an MCU or DMSA for various reasons.

The study was approved by the ethics committee of Children’s Hospital of Fudan University.

Examinations

All of the included patients accepted an acute DMSA renal scan and an MCU examination. The DMSA was performed first within 1 week after diagnosis, and the MCU was performed within 1 week after the infection was controlled. Prophylactic antibiotics were given orally for 3 days, with the MCU taking place on the second day.

DMSA scanning was performed following a standard protocol. For DMSA scanning, every patient was intravenously injected with 1.5 to 1.9 MBq/kg 99mTc (minimum was 11 MBq). Renal scintigraphy was performed 2 to 3 hours after the injection. The posterior and posterior oblique, parallel-hole, high-resolution images of both kidneys were acquired with the patient in a supine position. If needed, pinhole and single-photon emission computed tomography also were used for more accurate determination. The machine used is E-CAM Dual SPECT (Siemens Medical Solution, Hoffman Estates, IL). The results were considered normal if the uptake of the radioisotope was homogeneous with no evidence of scarring and relative uptake within the normal range (Fig 1). 9 DMSA scanning was considered to reflect an acute inflammatory process when at least 1 area of the decreased focal or diffuse cortical uptake of DMSA was noted with the renal outline preserved (Fig 2 A and B). If 1 or more focal renal cortical defects were consistently associated with the contraction of the renal outline, a renal scar was diagnosed (Fig 3). The results of renal scarring and acute inflammation were classified together as abnormal results. A kidney with a differential function ≤44% was also classified as abnormal.

The operating procedure of MCU was as follows: a 6-Fr feeding tube was inserted into the urethra and the residual urine was removed. A mixture of saline and contrast media was instilled, and the volume was calculated according to the child’s age and weight. To perform a safe MCU, 2 formulas are used in our hospital for the bladder volume estimation in children according to their age and weight: (1) age <1 year, bladder volume (mL) = 38 + (2.5 × age [months]); (2) age >1 year, bladder volume (mL) = (age [year] + 1) × 30. By combining their respective weights, the volume of contrast would then be slightly adjusted. The injection was also stopped as soon as the patient expressed an intense desire to micturate or when the urine began to drop from urethral meatus. Afterward, the 6-Fr feeding tube was removed. Dynamic images were taken during and after micturition to demonstrate the presence or absence of VUR. The VUR on MCU was graded according to the international VUR classification (Fig 4).
FIGURE 1
Normal DMSA scan.

FIGURE 2
A, right acute pyelonephritis (APN); B, bilateral APN.
The interpretations of the DMSA and MCU were made by experienced nuclear medicine consultants and experienced radiologists unaware of the patients’ clinical presentation. The DMSA and MCU examinations were performed in strict accordance with the previously mentioned standard procedures, and no adverse effects were observed.

Grouping
For the purposes of comparing the grading of VUR and the association of renal damage, grades I and II were grouped together as low-grade VUR, grade III to V as dilating VUR, and children without VUR were assigned to the group of non-VUR. In patients with bilateral VUR, the most severe grade was assigned.

The 2007 guidelines of the National Institute for Health and Clinical Excellence suggested more selective imaging strategies for children with high risk, which were aimed at more targeted investigations for children with high-risk factors. In the guidelines, the ages used as a dividing point were 6 months and 3 years old. The patients of our study were children ≤2 years old so they were divided into <6 months and ≥6 months age groups according to their ages of onset. We chose 6 months as the boundary to identify whether significant differences exist in the accuracy of DMSA in predicting dilating VUR between these 2 groups.

Statistical Analysis
All of the data were recorded on Excel spreadsheets. The statistical analyses were performed by using Stata version 10.0 (Stata Corp, College Station, TX). The Pearson $\chi^2$ test was used for comparing the groups, considering a $P < .05$ as statistically significant. The sensitivity, specificity, negative predictive value, positive predictive value, and likelihood ratios (LRs) with 95% confidence intervals (CIs) were calculated.

RESULTS
Basic Information of Patients Included
A total of 753 pediatric patients with UTI were found from January 2000 to December 2011. Fifty-five children were first excluded for diagnosing with other types of urinary abnormalities (renal duplication, 9 children; hydronephrosis, 15 children; pyeloureteral junction stenosis, 5 children; renal agenesis, 10 children; cystic kidney, 4 children; posterior urethral valve, 6 children; renal calculus, 4 children; ectopic kidney, 2 children). Another 175 children failed to complete the MCU and/or DMSA investigations, and thus were excluded, with
FIGURE 4
VUR of Grades I to V.
a mean age of 6.88 months and a gender ratio of 1.5:1.0. Among the 175 excluded patients, 72 were evaluated for the presence of VUR, of which 63 (87.5%) were dilating VUR and the other 9 were low-grade VUR; however, none of them had DMSA scan results.

As a result, only 523 children were eligible for inclusion into the study. Of the 523 patients, there were 301 boys and 222 girls, with a male:female ratio of 1.36:1.00. Their mean age was 7.47 months (range 1.1–24.0 months).

Comparison Between Different Grades of VUR

MCU detected VUR in 178 patients (34.0%, 86 boys and 92 girls): 27 were low-grade VUR, 151 dilating VUR (151/523 = 28.9%). In terms of renal units, 186 had dilating VUR, which accounts 17.8% of the 1046 kidneys.

DMSA showed abnormal results in a total of 397 children (75.9%), in whom a renal scar was found in 8.8% (46/523) (in terms of patients). Of all patients with abnormal DMSA results, 233 patients were in the non-VUR group (233/345 = 67.5%), 15 in the low-grade VUR group (15/27 = 55.6%), and 149 in the dilating VUR group (149/151 = 98.7%) (Table 1).

No significant differences were found when comparing the rate of abnormal DMSA results for non-VUR with the rate of the low-grade VUR group ($\chi^2 = 1.62, P = .20$). The rate of abnormal DMSA results for the dilating VUR group was significantly higher than the rates of the non-VUR group and the low-grade VUR group (dilating versus non-VUR $\chi^2 = 57.53, P < .01$; dilating versus low-grade $\chi^2 = 58.77, P < .01$).

Comparisons Between Different Age Groups

Taking 6 months old as the boundary, we compared the accuracy of DMSA in predicting dilating VUR between these 2 age groups and between boys and girls.

Age <6 Months

There were a total of 220 infants in the <6 months age group. The percentage of dilating VUR was 23.6% (52/220), and the rate of abnormal DMSA was 66.8% (147/220). The evaluation indices and their respective 95% CIs of DMSA for predicting dilating VUR in this group are listed in Tables 2, 3, and 4.

Age ≥6 months

There were a total of 303 children in the ≥6 months age group. The percentage of dilating VUR was 32.7% (99/303), and the rate of abnormal DMSA was 82.5% (250/303). The evaluation indices and their respective 95% CIs of DMSA for predicting dilating VUR in this group are listed in Table 5, 6, and 7.

Discussion

In this retrospective study, 34.0% of the patients with UTI had VUR diagnosed by MCU, which was similar to other reports. The rate of VUR in patients with abnormal DMSA was 41.3% (164/397), which was also in agreement with previous data. However, we noticed a relatively high percentage of dilating VUR (28.9% of patients; 187/1046 = 17.8% of renal units), which was higher than that reported in some studies, but was close to the proportion found in other reports.
TABLE 5 For Detecting Dilating VUR in Age ≥6 mo Group

<table>
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<tr>
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<th>DMSA</th>
<th>MCU</th>
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<tr>
<td></td>
<td>Grade III-V</td>
<td>Grade &lt;III*</td>
</tr>
<tr>
<td>+</td>
<td>99</td>
<td>151</td>
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<tr>
<td>–</td>
<td>0</td>
<td>53</td>
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<tr>
<td>Sum</td>
<td>99</td>
<td>204</td>
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</tbody>
</table>

Sensitivity 100.0% [100.0%–100.0%]
Specificity 25.98% [21.04%–30.92%]
PPV 39.60% [34.09%–45.11%]
NPV 100.0% [100.0%–100.0%]
LR+ 1.3510
LR– 0.0000

*, abnormal DMSA result; –, normal DMSA result; NPV, negative predictive value; PPV, positive predictive value.

* Grade <III includes patients without VUR and low-grade VUR.

TABLE 6 For Detecting Dilating VUR in Boys ≥6 mo

<table>
<thead>
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<th>DMSA</th>
<th>MCU</th>
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<tr>
<td></td>
<td>Grade III-V</td>
<td>Grade &lt;III*</td>
</tr>
<tr>
<td>+</td>
<td>55</td>
<td>81</td>
</tr>
<tr>
<td>–</td>
<td>55</td>
<td>109</td>
</tr>
</tbody>
</table>

Sensitivity 100.0% [100.0%–100.0%]
Specificity 34.25% [25.65%–42.85%]
PPV 47.83% [38.77%–56.88%]
NPV 100.0% [100.0%–100.0%]
LR+ 1.5209
LR– 0.0000

*, abnormal DMSA result; –, normal DMSA result; NPV, negative predictive value; PPV, positive predictive value.

* Grade <III includes patients without VUR and low-grade VUR.

TABLE 7 For Detecting Dilating VUR in Girls ≥6 mo

<table>
<thead>
<tr>
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<th>DMSA</th>
<th>MCU</th>
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<tbody>
<tr>
<td></td>
<td>Grade III-V</td>
<td>Grade &lt;III*</td>
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<tr>
<td>+</td>
<td>44</td>
<td>70</td>
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<tr>
<td>–</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Sum</td>
<td>44</td>
<td>95</td>
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</table>

Sensitivity 100.0% [100.0%–100.0%]
Specificity 26.32% [19.00%–33.64%]
PPV 38.60% [30.50%–46.69%]
NPV 100.0% [100.0%–100.0%]
LR+ 1.3572
LR– 0.0000

*, abnormal DMSA result; –, normal DMSA result; NPV, negative predictive value; PPV, positive predictive value.

* Grade <III includes patients without VUR and low-grade VUR.

The large number of cases of dilating VUR in our country may be due to several reasons. The detection rate of hydronephrosis by prenatal ultrasound is rather low in our country, and there is a lack of specialists to follow and manage these types of patients. Meanwhile, in other countries, children with hydronephrosis are identified by prenatal ultrasound with a high sensitivity, and thus intervention could be given earlier, which significantly decreases the number of patients with dilating VUR. Montini et al21 reported only 3 children exhibiting grade IV reflux and 1 child with grade V reflux in 300 patients with febrile UTI in Italy. Additionally, the management of febrile UTI in our country has not yet been standardized. Many patients with recurrent UTI have not yet undergone imaging examination of the urinary tract. A percentage of 8.8% renal scar was found through this study.

In this study, the proportion of dilating VUR and the rate of abnormal DMSA scanning increased with age instead of decreasing. The proportion of dilating VUR in the <6 months age group was 23.6% (52/220) and its rate of abnormal DMSA scanning was 66.8% (147/220). The proportion of dilating VUR in the ≥6 months age group was 32.7% (99/303) and its rate of abnormal DMSA scanning was 82.5% (250/303). For children with their first febrile UTI in our country, more emphasis should be placed on the initial imaging examination, even in the group older than 6 months. However, if all imaging studies are performed for all of the patients with the first febrile UTI, this would certainly place a burden on health resources and increase its costs.

As a noninvasive test, renal ultrasound has also been widely used for patients with febrile UTI for assessing the gross anatomy of the urinary tract.14,22 However, ultrasonography is not sensitive enough to detect the presence of vesicoureteral reflux and acute pyelonephritis. For acute febrile UTI, we believe that the prioritization of imaging strategy should be focused on the early identification of renal lesions to prevent further deterioration. DMSA possesses great value in detecting renal lesions. If the kidneys have already been affected, further examinations would be needed to identify whether risk factors such as VUR exist.

Clinically, for low-grade VUR, previous randomized controlled trials showed that antibiotic prophylaxis conferred no benefit in the rates of spontaneous resolution, UTI recurrence, or renal scarring.23–25 A recent study showed that low-grade VUR itself would not cause an increased incidence of scarring.21 For dilating VUR, characterized by a low rate of spontaneous resolution and a high probability for affecting the kidneys,26,27 antibiotic prophylaxis has been shown to be beneficial in preventing recurrent febrile UTIs and renal scarring in the prospective, randomized Swedish Reflux Trial.28 Therefore, the detection of dilating VUR is more important.

Compared with children with low-grade or no VUR, patients with dilating VUR are more likely to have their kidneys affected. In this study, it was found that regardless of age, the sensitivities of DMSA in predicting dilating VUR were very high (96.15% and 100.0% for <6 months and ≥6 months, respectively). When we analyzed the sensitivities together with each negative predictive value (97.26% and 100.0%) and LR (0.0911 and 0.0000), it could be concluded that the possibility of detecting dilating VUR on MCU is rather low when the result of DMSA is negative. In addition, no significant differences were found between boys and girls of both age groups, which suggests that the accuracies of the DMSA scan in predicting dilating VUR did not vary with gender. Therefore, we propose that DMSA at the acute phase should offer an advantage in avoiding unnecessary imaging, such as MCU. Furthermore,
a normal DMSA study should lessen the possibility of an acute pyelonephritis and dilating VUR.

According to the results, if DMSA shows an abnormal result, the MCU should be considered for further examination; if DMSA shows a normal result during the acute phase, MCU could be suspended temporarily. But to avoid a missed diagnosis, parents should be aware of the possibility of a recurring UTI and be advised to seek prompt treatment of any suspected reinfection.14 This viewpoint is consistent with that of other recent studies,4,6,17,20,29 all of which used the same top-down approach as well. It is worth emphasizing that the high sensitivity of the DMSA scan for the detection of dilating VUR in this study was because the scan was performed acutely within 1 week of the diagnosis. In our study, 126 of 523 MCUs would have been unnecessary, as only 2 patients with dilating VUR were missed. Recently, a meta-analysis resulted in the opposite conclusion that acute-phase DMSA renal cortical scintigraphy cannot be regarded as an accurate test for the identification of dilating VUR in children with their first febrile UTI.30 There are several reasons for this discrepancy. Compared with patients from the studies included in the meta-analysis, our study sample is highly heterogeneous and it may have included children with recurrent UTIs as well. The different inclusion criteria for patients may have played a role in leading to the opposite conclusion. DMSA was performed within 1 week after diagnosis in our study. The early time point when DMSA was performed during the acute phase may have increased the rate of DMSA scans with abnormal findings.6,29 In the studies included in the meta-analysis, most DMSA scans were performed within 5 days, some were performed within 2 weeks, and the latest scans were performed within 3 months after the UTI. Previous animal experiments showed that DMSA images were different at the different time points of infection and were also influenced by the time at which antibiotic treatment was initiated.31 However, Fouzas et al5 believed that an early DMSA scan would increase its rate of false-positive results. In our study, it was found that the false-positive rate was 57.7% (97/168) for <6 months and 74.0% (151/204) for ≥6 months of age, which were both very high. However, what cannot be ignored is that DMSA itself has false-negative results as well. Multidetector row computed tomography showed hidden lesions of acute pyelonephritis, which were undetectable with the DMSA scan in children.32 More studies are needed to identify the best time point for an acute DMSA scan and whether significant differences in the DMSA images exist at different time points. Finally, the methodology and image quality of DMSA are also problems worthy of concern. Although the same imaging guidelines were provided, the DMSA image quality varied more significantly than expected between institutions.33 The variations surely have an effect on the accuracy of DMSA in predicting dilating VUR. In our study, DMSA scans were all performed at the same center, which diminished the possible variations.

Our study has some limitations. First, we acknowledged the high drop-out rate of 23% (175/753) in our study. Exclusion of subjects who did not receive MCU or DMSA may pose a selection population bias. Although the mean age and gender ratio of the 175 excluded patients were similar to that of the included patients, the proportion of dilating VUR (87.5%) was higher than that of the included patients (28.9%). However, the sensitivity of DMSA in predicting dilating VUR might not be reduced, for a higher sensitivity could be achieved for the patients with a higher proportion of dilating VUR. Second, as mentioned previously, the population included in this study was heterogeneous, which was determined by the socioeconomic conditions of our region. Because the subjects included children with recurrent UTIs as well, it surely increased the proportion of patients with abnormal results of DMSA, thus increasing the sensitivities of DMSA scan to predict dilating VUR. Finally, the retrospective nature of data collection could be seen as another limitation. A finely designed diagnostic accuracy study is needed to validate the finding of this study.

CONCLUSIONS

For children ≤2 years of age with a febrile UTI, an acute DMSA scan is valuable in the exclusion of dilating VUR. The likelihood of the presence of dilating VUR on MCU is rather low when the result of DMSA is negative. DMSA should be conducted to assess the need for an MCU.

REFERENCES


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