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ORIGINAL ARTICLE

Reappraisal of the effectiveness of ^{99m}Tc-dimercaptosuccinic acid scans for selective voiding cystourethrography in children with a first febrile urinary tract infection

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Abstract Recent studies have yielded conflicting results regarding the ability of technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scans for identifying high-grade vesicoureteral reflux (VUR) in children with a first febrile urinary tract infection (UTI). This study aimed to reevaluate the effectiveness of ^{99m}Tc-DMSA renal scans for selective voiding cystourethrography (VCUG) in children with a first febrile UTI. The medical records of children aged $\leq$ 5 years who were admitted with a first febrile UTI were retrospectively reviewed. Ultrasonography (US) and DMSA renal scans were performed within 3–5 days after admission, and VCUG was performed 7–10 days after antibiotics treatment. A total of 653 children were enrolled for analysis, including 579 patients aged $<$ 2 years (Group A) and 74 patients aged 2–5 years (Group B). In Group A, DMSA scans were abnormal for 346 patients (59.8%), and normal for 233 patients (40.2%). High-grade VUR was present in 99 of 346 patients (28.9%) with abnormal DMSA scans, but present in only 16 of 233 patients (6.9%) with normal DMSA scans ($p < 0.001$). Regarding the prediction of high-grade VUR, the sensitivity and negative predictive value (NPV) for the DMSA scans were 86.1% and 93.1%, respectively. In Group B, DMSA scans were abnormal for 36 patients (48.6%), and normal for 38 patients (51.4%). High-grade VUR was present in 12 of 36 patients (33.3%) with abnormal DMSA scans, whereas none of the 38 patients with normal DMSA scans had high-grade VUR ($p < 0.001$). The sensitivity and NPV of the DMSA scans were both 100%. Using the selective VCUG strategy, approximately 40% of Group A patients and

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50% of Group B patients could be spared an unnecessary VCUG, respectively. Our study results suggest that ^{99m}Tc-DMSA renal scans are effective in identifying children with a first febrile UTI for selective VCUG.

Introduction

Controversy exists regarding which imaging studies are necessary for evaluation of the first febrile urinary tract infection (UTI) in young children [1]. The earlier guidelines issued by the American Academy of Pediatrics (AAP) recommended that infants and young children from 2 months to 2 years of age with UTI should undergo ultrasonography (US) and either voiding cystourethrography (VCUG) or radionuclide cystography (RCN), based on the assumption that vesicoureteral reflux (VUR) was the main risk factor in children with UTI [2]. However, subsequent studies have raised doubts regarding the clinical importance of VUR and the necessity of routine VCUG [3,4]. Therefore, there has been a recent trend toward the more selective use of VCUG in children with a first febrile UTI [1].

For decades, technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scans have been proven to be a sensitive imaging method for the diagnosis of acute pyelonephritis (APN) and renal cortical scars [5–9]. Several recent studies have demonstrated that children with negative ^{99m}Tc-DMSA renal scans during their first febrile UTIs rarely had high-grade VUR, and a strategy to perform VCUG in only patients with renal lesions has been proposed [10,11]. By contrast, certain authors have suggested that ^{99m}Tc-DMSA renal scans had a limited ability in identifying VUR and should not be endorsed as a replacement for VCUG [12,13]. In addition, most studies have focused on infants and children younger than 2 years of age, and the strategy in older children has rarely been discussed [8,9]. Therefore, the aims of this study were to reassess the effectiveness of ^{99m}Tc-DMSA renal scans for predicting selective VCUG in infants and children younger than 2 years of age, and to evaluate the potential application of DMSA scans in children aged 2–5 years.

Patients and methods

We retrospectively reviewed the medical records of all children aged $\leq$ 5 years who were admitted to our Department of Pediatrics with a first febrile UTI between March 2005 and February 2008. All children fulfilled the following criteria: (1) fever: body temperature $\geq$ 38°C; (2) abnormal urinalysis: positive leukocyte esterase and/or nitrite test, white blood cell count $>$ 5 cells/high-power field with or without bacteria in the urine; and (3) positive urine culture: growth of bacteria $>$ 10,000 colony-forming units/mL from urine samples obtained using bladder catheterization or any growth of bacteria from urine samples obtained using suprapubic bladder aspiration. Children with a known history of UTI, VUR, neurogenic bladder, or other congenital urinary tract anomalies were excluded. All children were treated with appropriate antibiotics. Renal and bladder ultrasonography and ^{99m}Tc-DMSA renal scans were performed as soon as possible after the diagnosis of UTI was confirmed, usually within 3–5 days after admission. VCUG was typically performed 7–10 days after appropriate antibiotics treatment. Informed consent was obtained from parents after the aims, benefits, and potential risks of these imaging studies were fully explained.

^{99m}Tc-DMSA renal scans were performed 2–3 hours after intravenous injection of 0.05 mCi/Kg (1.85 MBq/kg) ^{99m}Tc-DMSA with a minimal dose of 0.5 mCi (18.5 MBq). High-resolution images of anterior and posterior views of both kidneys together (500,000 counts per image) were acquired using a scintillation camera (Millennium MPR, General Electric) equipped with a high-resolution parallel-hole collimator. Relative renal function was calculated based on the geometric mean of the anterior and posterior radioactivity of each kidney. Magnified images of the posterior and posterior oblique views of each kidney (200,000 counts per image) were then acquired using a pinhole collimator. The renal images were interpreted by an experienced nuclear physician. Single and multiple areas with varying degrees of diminished cortical uptake of ^{99m}Tc-DMSA without loss of volume were interpreted as APN. Kidneys with diffusely reduced uptake and kidneys with relative renal function $<$ 44% were also classified as abnormal.

VCUG was performed according to the standard procedures of the Department of Pediatric Radiology, and the results were interpreted by an experienced pediatric radiologist. VUR was graded according to the recommendations of the International Reflux Study in Children [14]. Children with dilating VUR (Grades III to V) were defined as having high-grade VUR. For children with bilateral VUR, the higher grade of VUR of bilateral renal units was recorded.

We conducted statistical analyses by using R software (version 3.0.2). Fisher's exact test was used for comparison between dichotomous values and the Cochran-Mantel-Haenszel χ^2 test was used for comparison between ordered values. The diagnostic performance of ^{99m}Tc-DMSA renal scans for predicting high-grade VUR was determined by calculating the sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio with 95% confidence intervals.

Results

Tables 1 and 2 list in summary form the results of our study. There were 702 eligible patients during the study period. However, 49 children were excluded because their parents refused VCUG and these children therefore were lost to

Table 1 Findings of dimercaptosuccinic acid renal scans and voiding cystourethrography in Group A (age < 2 years), Group B (age 2—5 years), and the whole group.

	DMSA abnormal		DMSA normal		Total
	VUR present[a]	VUR absent[b]	VUR present	VUR absent	
Group A	99 *	247	16 *	217	579
Group B	12 *	24	0 *	38	74
Whole group	111 **	271	16 **	255	653

* $p < 0.001$, Fisher's exact test.
** $p < 0.001$, Cochran-Mantel-Haenszel χ^2 test.
DMSA = dimercaptosuccinic acid; VUR = vesicoureteral reflux.
[a] Grade III—V VUR.
[b] No VUR or Grade I—II VUR.

follow-up. A final 653 children were enrolled for analysis (the overall adherence to the clinical protocol was 93.0%). Among the enrolled children, 579 children were aged < 2 years (Group A) and 74 children were aged 2—5 years (Group B).

In Group A, 376 patients were boys and 203 patients were girls, with a median age of 4.5 months (range, 0.5—24 months). High-grade VUR was present in 115 patients (19.9%). The results of the ^{99m}Tc-DMSA renal scans were abnormal for 346 patients (59.8%), and normal for 233 patients (40.2%). In total, 99 of 346 patients (28.9%) with abnormal DMSA scans had high-grade reflux, whereas only 16 of 233 patients (6.9%) with normal DMSA scans had high-grade reflux ($p < 0.001$). The sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio of ^{99m}Tc-DMSA renal scans for predicting high-grade VUR were 86.1%, 46.8%, 28.9%, 93.1%, and 5.44, respectively. By implementing a selective VCUG strategy—performing VCUG in only patients with abnormal DMSA scans and refraining from performing VCUG in patients with normal DMSA scans unless recurrent UTIs occurred, the number of VCUG patients would be reduced by approximately 40%. Of the 16 children with normal DMSA scans and high-grade reflux, 10 received prophylaxis with antibiotics and their VUR resolved spontaneously, one received deflux injection according to the decision of their clinician and parents, and five patients experienced breakthrough infections in spite of antibiotics prophylaxis and DMSA scans during admission showed APN. The most likely explanation was a combination of preexisting high-grade VUR and more virulent bacteria during the second infections. Finally, these five patients underwent an operation for correction of their VUR.

In Group B, 19 patients were boys and 55 patients were girls, with a median age of 3 years and 4 months (range, from 2 years and 1 month to 5 years). High-grade VUR was present in 12 patients (16.2%). The results of the ^{99m}Tc-DMSA renal scans were abnormal for 36 patients (48.6%), and normal for 38 patients (51.4%). In total, 12 of 36 (33.3%) patients with abnormal DMSA scans had high-grade reflux, whereas none of the 38 patients with normal DMSA scans had high-grade reflux ($p < 0.001$). The sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio of ^{99m}Tc-DMSA renal scans for predicting high-grade VUR were 100%, 61.3%, 33.3%, 100%, and 39.29, respectively. A selective VCUG strategy would reduce the number of patients with VCUG by approximately 50%.

For the whole group, the sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio of ^{99m}Tc-DMSA renal scans for predicting high-grade VUR were 87.4%, 48.5%, 29.1%, 94.1%, and 6.53, respectively. There was a significantly higher percentage of high-grade VUR among patients with abnormal DMSA scans (29.1%) than those with normal DMSA scans (5.9%; $p < 0.001$).

Discussion

In addition to showing that ^{99m}Tc-DMSA renal scans were sensitive for the diagnosis of APN and renal cortical scars, early studies also suggested that evaluation with DMSA scan at the time of acute infection should precede and determine

Table 2 Diagnostic performance of DMSA renal scans for prediction of high-grade VUR in Group A (age < 2 years), Group B (age 2—5 years), and the whole group.

	Group A	Group B	Whole group
Sensitivity	86.1 (78.4—91.8)[a]	100 (64.0—100)	87.4 (80.4—92.6)
Specificity	46.8 (42.2—51.4)	61.3 (48.1—73.4)	48.5 (44.1—52.8)
Positive predictive value	28.9 (23.9—33.7)	33.3 (18.6—51.0)	29.1 (24.6—33.9)
Negative predictive value	93.1 (89.1—96.0)	100 (86.5—100)	94.1 (90.6—96.6)
Odds ratio	5.44 (3.11—9.50)	39.29[b] (2.22—694.08)	6.53 (3.76—11.33)

All values except odds ratio are presented as %.
DMSA = dimercaptosuccinic acid; VUR = vesicoureteral reflux.
[a] 95% confidence intervals.
[b] Corrected odds ratio.

the need for further evaluation of VCUG [8,9,15]. The imaging recommendations from the European Society of Pediatric Radiology advocated ultrasonographic examination of all pediatric UTI patients, and if the ultrasound was normal and there was clinical suspicion for APN, an early DMSA scan was performed. Further investigations, including VUR assessment and bladder function studies, were indicated only in children with renal involvement or scar formation but no additional imaging was necessary in children without renal involvement or scarring and normal urinary anatomy [16]. This imaging strategy has often been referred to as a top-down approach because the initial diagnostic concern is renal involvement, instead of VUR; this strategy has remained one of the most commonly used imaging recommendations in recent years [17,18].

Numerous studies have evaluated the accuracy of acute-phase DMSA renal scans in identifying high-grade VUR in recent years, but have yielded conflicting results [10–13,19–23]. Hansson et al [10] found, in a retrospective analysis of 303 children younger than 2 years with initial UTI, that a normal DMSA scan and dilating VUR occurred in only seven infants. The authors suggested that DMSA scan in infants with UTI might replace VCUG as a first-line investigation, and proposed a strategy to perform VCUG only in patients with renal lesions [10]. A subsequent prospective study by Preda et al [11], enrolling 290 infants younger than 1 year with first diagnosed symptomatic UTI, further confirmed that DMSA scan results were abnormal in all 27 infants with dilating VUR except one. The authors concluded that a normal DMSA scan made VCUG unnecessary in the primary examination of infants with UTI [11]. By contrast, Fouzas et al [12] found that 12 of 296 children had dilating VUR, despite normal findings on both DMSA scan and ultrasonography. The authors suggested that acute DMSA scans had limited overall ability in identifying VUR, and should not be endorsed as a replacement for VCUG in the evaluation of young children with a first febrile UTI [12]. A recent meta-analysis showed that the pooled sensitivity and specificity of ^{99m}Tc-DMSA renal scans were 79% and 53%, respectively, for patient-based analysis in eight studies. The authors concluded that acute-phase ^{99m}Tc-DMSA renal scans cannot be recommended as a replacement for VCUG in the evaluation of young children with a first febrile UTI [24].

The results of our study showed that, in children aged $<$ 2 years, ^{99m}Tc-DMSA renal scans had a sensitivity of 86.1% and a negative predictive value of 93.1% for identifying high-grade VUR. These results were similar to those reported by Hansson et al [10] and were also comparable with several recently published studies [11,19,20,22,25]. Our study again confirmed that ^{99m}Tc-DMSA renal scans could be used to identify most children with high-grade VUR, and that the rate of high-grade VUR among children with negative DMSA scans was low [10,11]. It is important to note that, although variations in sensitivity were significant (54.5–100%) in the studies included in the recent meta-analysis, all studies except one consistently showed high negative predictive values (90.0–100%), as noted in our study [24]. From our viewpoint, the negative predictive value of DMSA renal scans is as critical as sensitivity. We believe that DMSA renal scans, with their high negative predictive value, are useful in selecting children with a first febrile UTI for VCUG. A selective VCUG strategy, according to DMSA renal scan findings, could reduce the number of VCUG patients by approximately 40%.

To the best of our knowledge, only a few studies have discussed imaging strategies for children older than 2 years [8,9]. In a subgroup of children aged 2–5 years, the results of our study showed that the sensitivity and negative predictive value of ^{99m}Tc-DMSA renal scans were both 100%, which was in line with those reported in previous studies [8,9]. Rosenberg et al [8] showed that 11 of 45 children younger than 4 years had significant reflux, and abnormal DMSA scan results identified 10 of these patients and a combination of US and DMSA scans identified all cases. Jakobsson et al [9] presented similar findings, and suggested that VCUG might be safely omitted as a routine investigation in children older than 1 year with a UTI who had a normal DMSA scan during infection or at follow up approximately 2 months after infection and a normal US during infection. As the incidence of high-grade VUR is expected to decline with age, a routine VCUG examination in children with negative DMSA scans could be even less favorable. Although the sample was small, because we included only patients with a first febrile UTI, our preliminary data suggested that DMSA renal scans were effective for predicting selective VCUG, and could reduce the number of VCUG patients by approximately 50%. Further studies enrolling more cases are necessary to validate the clinical application of DMSA scans in this subgroup of patients.

Another question of clinical concern is, as indicated by Mantadakis et al [24], the consequences for children with dilating VUR who are not identified using ^{99m}Tc-DMSA renal scans. Biggi et al [26] showed that the risk of scarring in a low-risk group of patients (normal kidneys with/without VUR) was 0%, in contrast to an intermediate-risk group (mild lesions with/without VUR or extensive lesions without VUR) and a high-risk group (extensive lesions with VUR). Hansson et al [10] demonstrated that six of seven patients with dilating VUR and normal ^{99m}Tc-DMSA renal scans had normal DMSA scans at follow-up after 1–2 years, and VUR resolved spontaneously in five patients, and improved spontaneously to Grade I in two patients. Lee et al [21] also demonstrated that only one of 20 children with high-grade VUR who had normal results for both US and DMSA scans developed a new scar. These data suggested that the risk of scar development in children with normal ^{99m}Tc-DMSA renal scans was low, even with the presence of VUR.

Our study had certain limitations. First, some patients were excluded because their parents refused VCUG. This might have influenced the actual results of this study; however, it also reflected a real clinical scenario: parents are typically concerned regarding the invasiveness and discomfort of VCUG. The ^{99m}Tc-DMSA renal scan findings may be useful in clarifying the necessity of VCUG. Second, the sample in the subgroup of children age 2–5 years was small. Further prospective studies enrolling more patients are warranted to validate the clinical application of DMSA scans in this subgroup of children. Third, as a retrospective study, we did not know the actual outcomes of patients with normal DMSA renal scans and high-grade VUR if these were undetected and the patients did not undergo treatment. However, certain patients did have breakthrough

infections. Therefore, VCUG should be considered when recurrent infections are observed.

In conclusion, ^{99m}Tc-DMSA renal scans not only provide useful information regarding the extent and severity of APN but may also be effective in selecting children aged < 2 years with a first febrile UTI for selective VCUG; promising results were also obtained for children aged 2—5 years. With the selective VCUG approach, patients with normal DMSA scans are spared an unnecessary VCUG, unless recurrent UTIs are observed.

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