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Kidney Ultrasonography and Dimercaptosuccinic Acid Scans for Revealing Vesicoureteral Reflux in Children With Pyelonephritis: A 7-Year Prospective Cohort Study of 1500 Pyelonephritic Patients and 2986 Renal Units

Masoumeh Mohkam [1*], Saiid Maham [1], Alireza Khatami [2], Ilana Naghi [1], Babak Otukesh [1], Ahmad Reza Shamshiri [3], Mostafa Sharifian [1], Reza Dalirani [1], Fatemeh Abdollah Gorji [1]

[1] Pediatric Infections Research Center (PIRC), Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[2] Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[3] Tehran University of Medical Sciences, Tehran, IR Iran

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ABSTRACT

Background: The presence of vesicoureteral reflux (VUR) has been documented in 1.3% of the general population, 70% of infants with urinary tract infection (UTI), and 15–25% of children with UTI.
Objectives: The main aims of this prospective cohort study were to compare the efficiency of different imaging techniques [renal ultrasonography, cortical scintigraphy with technetium-99m dimercaptosuccinic acid (99mTc DMSA)] in detecting VUR in patients with acute pyelonephritis.
Patients and Methods: Between June 2003 and March 2010, we recruited a prospective cohort of patients aged 1 month to 14 years. Pediatric patients with documented urinary tract infections and imaging evidence of upper tract involvement were examined by DMSA scintigraphy, renal ultrasonography, and voiding cystourethrography (VCUG). The assessments included UTI profiling, kidney ultrasonography, and DMSA scans. Data were expressed as mean ± SD. Statistical tests were two-tailed and were considered significant when $P \leq 0.05$.
Results: A total of 1500 pediatric patients were eligible to receive treatment for pyelonephritis. DMSA scans were normal in 20.2% of the patients and abnormal in the remaining 79.8%, and the kidney ultrasonographies yielded normal results in 68.5% of the patients and abnormal results in the remaining 31.5%. There was a significant difference between the ultrasonography reports of patients with normal and abnormal DMSA scans. The VCUG results were normal in 74.1% of the patients and indicated VUR in the remaining 25.9% (VUR grade I in 10.7%, grade II in 7.3%, grade III in 4.7%, grade IV in 1.7%, and grade V in 1.5%). The refluxes were unilateral in 62.9% of the patients and bilateral in the remaining 37.1%. We found a significant correlation between the presence of VUR in VCUG and urological abnormality in ultrasonography ($r = 0.14$, $P < 0.001$). The incidence of VUR among patients showing severe abnormalities in DMSA scintigraphy, was significantly higher than that among patients with normal DMSA results or those showing mild to moderate changes in DMSA scintigraphy.
Conclusions: We concluded that kidney ultrasonography and DMSA scans can be performed before VCUG in children with UTI. In addition, we recommend performing VCUG in cases of pyelonephritis only when the patients show abnormal kidney ultrasonography or DMSA scan results.

* *Corresponding author:* Masoumeh Mohkam, Pediatric Infectious Research Center, Mofid children's hospital, Shahid Beheshti University of Medical Sciences, Shariati Ave, Tehran, IR Iran. Tel/Fax: +98-22227033,
E-mail: mohkam@pirc.ir

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▸ *Implication for health policy/practice/research/medical education:*
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1. Background

Previous studies have suggested that 7% of girls and 2% of boys will have a urinary tract infection (UTI) before 6 years of age (1). The presence of vesicoureteral reflux (VUR) has been documented in 1.3% of the general population. Further, the incidence of VUR is 70% in infants and 20–40% in children with the first febrile UTI (2). In general, VUR is more common in females, except in the case of infants, and most studies showed a male preponderance and more severe VUR in infants (3). Studies have revealed that VUR is the most common abnormality in UTI, and reflux nephropathy is an important cause of end-stage renal disease (ESRD) in pediatric patients (4). According to some previous studies, renal ultrasonography and DMSA scans are ineffective for screening VUR in children with UTI (5, 6); therefore, at present, VUR in children is detected by using cystography. However, researchers have been discussing the possibility of VUR-specific imaging findings in infants and children with UTI (7–10). With the major progress in ultrasonographic techniques, the efficacy of ultrasonography in detecting urological abnormalities like VUR in children needs to be reviewed, and this has recently been a question of debate (10).

2. Objectives

The main aim of this prospective study was to compare the sensitivities of different imaging techniques like renal ultrasonography and cortical scintigraphy with technetium-99m dimercaptosuccinic acid (99mTc DMSA) in detecting VUR in children with acute pyelonephritis.

3. Patients and Methods

Between June 2003 and March 2010, we recruited a prospective cohort of patients who aged from 1 month to 14 years, and constructed a database of the study group. Patients with documented urinary tract infection and clinical and paraclinical evidence of upper tract involvement were examined with DMSA scintigraphy, renal ultrasonography, and voiding cystourethrography (VCUG). Pyelonephritis was diagnosed on the following instances: positive urine culture or in patients with negative urine cultures, significant leukocyturia in febrile children with clinical (fever, vomiting, abdominal pain, dysuria, and anorexia) and paraclinical (leukocytosis more than 10000/hpf, positive CRP $\geq 1^{+}$ and increased ESR > 20 mm/hr) signs. Patients with suspected pyelonephritis were diagnosed by DMSA scintigraphy. Depending on the child's age, urine samples were obtained through suprapubic aspiration, clean catch bag, or clean midstream voiding. Glomerular filtration rate was calculated according to Schwartz' formula, and results were normal in all patients. Ultrasonographic studies were done by ESAOTE Au4-Idea in the same center and all of them were conducted by the same sonologist. DMSA scintigraphy studies were done in the same center and all were conducted by the same nuclear medicine specialist. Patients satisfying any of the following criteria were excluded from our study: any evidence of renal insufficiency, hypertension, previous surgical intervention or known urological problems, recent history of antibiotic administration, and concomitant extra renal infection. A total of 1500 pediatric patients were eligible to receive treatment for pyelonephritis according to our protocol. The ethics committee of the Shahid Beheshti Medical University and Pediatric Infectious Research Center approved this study. Data were expressed as mean ± SD. Statistics tests were two-tailed, and the results were considered significant when $P \leq 0.05$. Findings were compared using the Mann-Whitney U test and Pearson's correlation coefficient, and receiver operating characteristic (ROC) curves were used to determine sensitivity and specificity. We also obtained the negative predictive value, positive predictive value, and likelihood ratio for the different imaging methods. The SPSS statistical software program was used for statistical analyses.

4. Results

Between June 2003 and March 2010, a prospective cohort of patients aged 1 month to 14 years was recruited. We evaluated 1500 pyelonephritic patients and 2986 renal units (among our patients, 14 children had a single kidney). Demographic data of our patients are shown in *Table 1 and 2*. The results of this study showed that the study group had 76.8% female patients. DMSA scans were normal in 20.2% of the patients and abnormal in the remaining 79.8% (mildly reduced cortical uptake in 45%, moderately reduced cortical uptake in 12.3%, severe decreased cortical uptake in 12%, and scar formation in 10.5%).

Kidney ultrasonographies of the patients yielded normal results in 68.5% of the patients and abnormal results in the remaining 31.5% (mild hydronephrosis in 9.2%, moderate to severe hydronephrosis in 9.1%, stone formation in 3.1%, decreased cortical thickness in 1.5%, and other abnormalities in 8.8%). There was a significant difference between ultrasonography reports of patients with normal and abnormal DMSA scans ($P < 0.012$). However, no

Table 1. Demographic Data of the Study Group

	Minimum	Maximum	Mean	SD
Age, mo	1	170	36.17	33.87
Body weight, kg	1.7	78	27.8	24.7
Systolic blood pressure, mmHg	70	130	97.3	12.33
Diastolic blood pressure, mmHg	40	90	60.4	10
WBC	7500	23400	16820	10000
PMN	4000	9600	5160	2100
Hb [a]	7.5	12.1	10.89	3.7
MCV [a]	62	103	85.38	48.84
ESR [a]	12	129	40.15	29.26
BUN [a]	3	26	13	11.33
Cr [a]	0.2	1	0.65	0.5
U RBC	0	50	5	1
U WBC	2	80	19	18
U SG	1002	1038	1029	20
U PH	5	8	5.5	0.7

[a] Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume

Table 2. Chief Complaints in the Study Group

Chief Complaint	Frequency, No.	%
Fever	1245	83
Hematuria	530	35.3
Dysuria	231	15.4
Vomiting	183	12.2
Abdominal pain	121	8.1
Diarrhea	84	5.6
Frequency	81	5.4
Febrile convulsion	67	4.5
Malodor urine	35	2.3

such difference was seen in detection of scar formation between DMSA scan and ultrasonography. The VCUGs of patients showed normal results in 74.1% of the patients and VUR in 25.9% (VUR grade I in 10.7%, grade II in 7.3%, grade III in 4.7%, grade IV in 1.7%, and grade V in 1.5%). The refluxes were unilateral in 62.9% and bilateral in 37.1%. Frequency of scar formation was not significantly different in patients with or without reflux. The abnormalities detected by imaging are shown in *Table 3*.

We found a significant correlation between the presence of VUR in VCUG and urological abnormality in ultrasonography (r = 0.14, $P < 0.001$). Among patients showing severe abnormalities in DMSA scintigraphy, the percentage of VUR was significantly higher than that in patients with normal DMSA results or those showing mild to moderate changes in DMSA scintigraphy (46.3% *vs.* 26.9%). Severe abnormality in DMSA scintigraphy can predict the presence of VUR with a likelihood ratio of 1.08 [LR^+ = sn/(1-sp): 1.08 (1.02–1.16), LR^- = (1-sn)/sp: 0.71 (0.53–0.96)]. There was a significant correlation between changes in DMSA scintigraphy and the presence of VUR (r = 0.07, $P < 0.02$). The sensitivity of DMSA scans for the prediction of VUR was 84.1% (79.3–88.2) and the specificity was 22.4% (19.6–25.4). In addition, the positive predictive value (PPV) of DMSA was 26.9% (24.0–30.0) and its negative predictive value (NPV) was 80.6% (74.9–85.5).

5. Discussion

Our study showed a significant correlation between the presence of VUR in VCUG and urological abnormality in ultrasonography. In addition, among patients showing severe abnormality in DMSA scintigraphy, the percentage of VUR was significantly higher than that in patients with normal DMSA results or those showing mild to moderate changes in DMSA scintigraphy. In other words, severe abnormality in DMSA scintigraphy can predict the presence of VUR with a likelihood ratio of 1.08. The sensitivity of DMSA scans for VUR prediction was 84.1% (79.3–88.2) and the specificity was 22.4% (19.6–25.4). In addition, DMSA scans had a positive predictive value (PPV) of 26.9% (24.0–30.0) and a negative predictive value (NPV) of 80.6% (74.9–85.5). In the study by Zhang, the sensitivity of DMSA for detecting high-grade VUR was 99.0% and its negative predictive value was 99.1% (11). Lee *et al.* reported an NPV of 85.4% and PPV of 56.6% for DMSA scintigraphy in predicting VUR (12). Further, Jaukovic *et al.* determined that the PPV and NPV of abnormalities on DMSA scans were 43.94% and 90.38%, respectively, for detecting the high-grade reflux on VCUG. The positive likelihood ratio for the utility of DMSA in ruling out the presence of high-grade VUR on VCUG was 1.93 (13).

In general, VUR is the most common urological abnormality in patients with UTI, and it is one of the most frequent risk factors for the development of renal damage (10). Fouzas *et al.* studied 296 patients with UTI and concluded that DMSA scans have limited ability in identify-

Table 3. Abnormalities Detected by Imaging in Pyelonephritic Children

Imaging	Count, No.	%
Sonography		
Abnormality		
Normal	960	68.5
Fullness or Stasis	129	9.2
Hydronephrosis	127	9.1
Stone	43	3.1
Scar, Decrease Size	21	1.5
Others	123	8.8
Total results		
Normal	960	68.5
Abnormal	442	31.5
DMSA [a]		
Abnormality		
Normal	239	20.2
Mildly Decreased Cortical Uptake	533	45.0
Moderately Decreased Cortical Uptake	146	12.3
Severely Decreased Cortical Uptake	142	12.0
Scar/Defect/irregularity	124	10.5
Total results		
Normal	239	20.2
Abnormal	945	79.8
VCUG [a]		
Abnormality		
Normal	921	74.1
VUR Grade 1	133	10.7
VUR Grade 2	91	7.3
VUR Grade 3	58	4.7
VUR Grade 4	21	1.7
VUR Grade 5	19	1.5
Total results		
Normal	921	74.1
Abnormal	322	25.9

[a] Abbreviations: DMSA, dimercaptosuccinic acid; VCUG, voiding cystourethrography

ing VUR, and VCUG should not be replaced with DMSA scans in the evaluation of patients with their first episode of pyelonephritis (6). Previous studies in neonates have shown that the use of kidney ultrasonography alone has limitations in detecting VUR (14). During the physiological transition from the neonatal period to infancy, a considerable proportion of VUR cases show spontaneous resolution; therefore, there is debate over the approach of performing VCUG in all patients with pyelonephrosis. At present, most pediatric societies recommend performing VCUG for all patients with their first febrile UTI (15–17). An interesting observation is that the results of VCUG are normal in 60% to 80% of these patients (18). As a whole, VCUG itself is an invasive test and has been associated with a risk of iatrogenic infection and exposure to radiation (19). Moreover, a recent study of infants with their first UTI showed that only 40% of patients underwent VCUG (20). This result means that the VCUG procedure is unpleasant for physicians, patients, and their parents, and that pediatricians apply implicit criteria while selecting patients for VCUG. Studies suggest that prediction of the absence of VUR would help avoid unnecessary cystography (21). There have been various studies on pediatric patients with UTI, who underwent kidney ultrasonography, DMSA renal scintigraphy, or assessments for other inflammatory markers that served as prediction factors for VUR. Some of these reports and their findings are discussed here. Wang showed that the sensitivity and specificity of renal ultrasonography in detecting VUR were 24.8% and 94.3%, respectively (22). Leroy *et al* reported that high serum procalcitonin level is a strong and validated predictor of vesicoureteral reflux, and can be used to identify low-risk patients with VUR to avoid unnecessary VCUG (14). Previous studies in the pediatric group have also revealed that patients with pyelonephritis and accompanying VUR rarely show normal results in DMSA scanning and kidney ultrasonography. On the basis of these findings, the need for selective application of VCUG has been emphasized (23–25). Tseng *et al.* stated that children showing negative results in a renal DMSA scan in the acute phase of UTI, rarely have VUR and may never have high-grade VUR. They proposed

that voiding VCUGs in children with negative DMSA renal scans could significantly reduce the use of this potentially traumatic test (7). Based upon the other query, because of its invasiveness and exposure to radiation, VCUG for all children with pyelonephritis has not been considered, and there is no consensus regarding this subject (10). Preda *et al.* showed that DMSA scintigraphy shows abnormal results in patients with dilating VUR, so they proposed that normal DMSA scans can make VCUG unnecessary in infants with UTI (26). Further, in our earlier study on this topic, we suggested that a negative result on a 99mTc-DMSA scan can be used to skip VCUG, which is important to decrease the use of this procedure and also its complications (27). In the study by Sharbaf Ghane, Follow-up voiding cystourethrogram revealed resolution of VUR in 55% and improvement in 27.5% of the patients (28). Sharifian *et al.* showed that spontaneous resolution of VUR was observed in 39% of the patients, and the mean time to spontaneous resolution in their study was 1.5 ± 1 years (29). In addition, Lee *et al.* revealed that in due course of time, most of the low-grade VURs with normal DMSA scans and kidney ultrasonography were resolved or downgraded spontaneously. They also demonstrated that most high-grade VURs could be detected by US and DMSA scan; therefore, they recommended that the physician can anticipate spontaneous improvement in patients with either low- or high-grade reflux if the results of kidney ultrasonography and DMSA scan were in the normal range (12). The results of other recent studies in this regard demonstrated that in infants with the first episode of pyelonephritis, VCUG might be performed on those who show abnormalities in kidney ultrasonography or DMSA renal scan, and in patients with repeated pyelonephritis or deterioration of renal function. Ljiljana Jaukovic *et al.* evaluated 118 children who underwent VCUG and late DMSA scan due to pyelonephritis, and recommended performing VCUG only on pyelonephritic patients with abnormal results in DMSA scans (13). Moreover, Zhang *et al.* showed that DMSA scan can predict high-grade VUR in a majority of pyelonephritic children, and they recommended that DMSA scans be used before VCUG in children with UTI (11). Another study from Japan showed that VCUG should not be used as the first-line test to rule out renal damage caused by UTI and recommended a more selective approach with VCUG being reserved for pediatric patients with scarring or other abnormalities on DMSA scans (30). Furthermore, a study conducted by Alonso Usabiaga concluded that technological advances in ultrasonography have allowed DMSA to be the primary imaging technique for the management of VUR in pediatrics (31).

Although many clinicians believe that VCUG is at present the most sensitive method to detect VUR, our study revealed that the abnormalities in ultrasonography and DMSA scans can predict the presence of VUR in VCUG. Considering the non-invasive nature of ultrasonography, in addition to the absence of radiation exposure during ultrasonography, the general availability and lower cost of this method, and the higher number of experienced ultrasonography operators, we recommend it as a first line investigation in urinary tract infection and as a screening test for VUR, (if the examination is performed by an experience sonologist). In addition, the non-invasive nature of DMSA and the low radiation levels in DMSA scanning make it an acceptable and fair alternative test for VUR in pediatric patients. Further studies will be needed to establish whether ultrasonography and/or DMSA scan are sufficient for prediction or detection of VUR in pyelonephritic patients.

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