

Technetium Tc 99m Dimercaptosuccinic Acid Renal Scintigraphy in Diagnosis of Urinary Tract Infections in Children with Negative Culture

Ahmad Ali Nikibakhsh,¹ Zahra Yekta,² Hashem Mahmoodzadeh,¹ Mohammad Karamiyar,¹ Mehdi Fazel³

Introduction: The aim of this study was to evaluate the accuracy of Technetium Tc 99m dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scintigraphy in the diagnosis of urinary tract infection (UTI) in children with suspected infection but with a negative urine culture.

Materials and Methods: The records of all children with suspected or definite diagnosis of UTI presented during a 2-year period were reviewed in this study. Abnormal findings on renal scintigraphy, voiding cystourethrography (VCUG), and ultrasonography were evaluated and compared between the patients with the definite diagnosis of UTI and those with suspected UTI and negative urine cultures.

Results: Of 210 patients, 86 had a definite diagnosis of UTI (group 1) and 124 had suspected UTI without a positive culture (group 2). Abnormal findings on DMSA scans were seen in 76 patients (88.4%) in group 1 and 84 (67.7%) in group 2. Vesicoureteral reflux was detected by VCUG in 50% and 32.3% of the patients in groups 1 and 2, respectively. In group 2, vesicoureteral reflux was seen in 40.5% of the patients with abnormal DMSA scan. Ultrasonography findings were abnormal in 51.3% and 39.8% of the patients with abnormal DMSA scan findings in groups 1 and 2, respectively.

Conclusion: According to our findings, in children with a negative urine culture and abnormal urinalysis, ^{99m}Tc-DMSA renal scintigraphy is helpful in diagnosing UTI and vesicoureteral reflux; we recommend VCUG when DMSA scan supports UTI despite a negative urine culture and a normal ultrasonography.

Keywords: urinary tract infection, vesicoureteral reflux, dimercaptosuccinic acid scan

*Urol J (Tehran). 2006;3:139-44.
www.uj.unrc.ir*

INTRODUCTION

Urinary tract infection (UTI) is considered as a complicated disease in childhood and its recurrence may result in damage to the kidneys, finally leading to chronic kidney disease at puberty.⁽¹⁻⁵⁾

The symptoms of UTI are nonspecific in children (including malnutrition, diarrhea, vomiting, restlessness, and failure to thrive). On the other hand, urine sampling from most children is difficult in outpatient

settings. Therefore, the diagnosis of UTI with the classic criteria used for adult patients is not always possible in children. This may lead to missed diagnosis of UTI in this group of patients.^(4,6-8)

Furthermore, in young ages, the probability of damage to the kidney parenchyma is high and it may result in irreversible complications. Thus, early diagnosis of UTI requires more sensitive techniques. Renal Scintigraphy using Technetium Tc

¹Department of Nephrology, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran

²Department of Social Medicine, Urmia University of Medical Sciences, Urmia, Iran

³Department of Nuclear Medicine, Imam Khomeini, Urmia University of Medical Sciences, Urmia, Iran

Corresponding Author:
Ahmad Ali Nikibakhsh, MD
Pediatric Nephrology Department,
Emam Khomeini Hospital, Urmia, Iran
Tel: +98 441 346 1524
E-mail: anikibakhsh@yahoo.com

Received October 2005
Accepted May 2006

^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) is one of the imaging methods with a significant role in the diagnosis of both acute pyelonephritis and its complications on the kidney parenchyma.⁽⁹⁻¹⁶⁾ Suprapubic sampling is not a routine technique for detection of UTI in out-patient setting; therefore, ^{99m}Tc-DMSA renal scintigraphy may be helpful in children at the risk of kidney scarring.^(17,18) The aim of this study was to evaluate the accuracy of this technique in the diagnosis of UTI in children with suspected infection but a negative urine culture.

MATERIALS AND METHODS

The records of all children with a suspected or definite diagnosis of UTI presented to Imam Khomeini Hospital of Urmia between 2000 and 2002 were reviewed in this study. The children were divided into groups 1 and 2 based on the following characteristics:

Group 1 consisted of the children with the definite diagnosis of acute pyelonephritis according to the concurrent signs of an auxiliary temperature over 37.5°C, a positive urine culture for a microorganism with a colony count of 10⁵ or greater (using urine-bag sampling), and pyuria (more than 8 white blood cells per high-power microscopic field [HPF]). Group 2 consisted of the children with the diagnosis of UTI but a negative urine culture. Diagnosis had been made in the absence of the classic criteria in favor of UTI, with (1) nonspecific symptoms, (2) abnormal urinalysis results including more than 8 white blood cells per HPF solely or accompanied by microscopic hematuria, or more than 5 red blood cells per HPF solely or with pyuria, and (3) a colony count of less than 10² for a microorganism cultured in a urine-bag sample or the mixed/negative urine culture of the microorganisms.

For editorial comment see p 143

Reports of renal scintigraphy with ^{99m}Tc-DMSA were

reviewed and the results were considered abnormal if a significant decreased radioisotope uptake in the renal cortex (cortical inflammation) and obvious defects in the kidney contours (scar formation) were present.^(9,10) Voiding cystourethrography (VCUG) and ultrasonography (US) had been performed in all children of both groups. Voiding cystourethrography would be performed if DMSA scan and US revealed abnormal findings or if recurrent pyuria or microscopic hematuria (in more than 3 laboratory studies) were present.

The results of DMSA scan, VCUG, and US were compared between the 2 groups. The chi-square test was used for comparison of qualitative variables.

RESULTS

Of 210 patients, 86 had a definite diagnosis of UTI (group 1) and 124 had a suspected UTI without a positive urine culture (group 2).

In group 2, there were 35 boys (28.2%) and 89 girls (71.8%), with a mean age of 6.0 ± 1.7 years. Thirty-three (26%) patients were younger than 1 year old, 45 (33%) were 1 to 5, 35 (28%) were 6 to 10, and 11 (13%) were older than 10 years old. In this group, 84 patients (67.7%) had abnormal findings on DMSA scans (Table 1), of whom 22 (26.2%) were boys, 62 (73.8%) were girls, and 48 (57.1%) were 5 years old or younger. Vesicoureteral reflux (VUR) was detected by VCUG in 50% and 32.3% of the patients in groups 1 and 2, respectively (Table 1). Detection of VUR reached 40.5% in group 2 when DMSA scan was abnormal (Table 2). In addition, there were 34 children in group 2 with normal DMSA scan and US that only 3 of them had VUR. Reflux grades in the patients of group 2 are demonstrated in Table 3.

Ultrasonography findings were abnormal in 51.3% and 39.8% of the patients with abnormal DMSA scan in groups 1 and 2, respectively (Table 4). The detected abnormalities on US of the patients in group 2 are shown in Table 5.

Table 1. Results of Diagnostic Tools in Patients with Definite Diagnosis of UTI (Group 1) and Those with a Suspected UTI (Group 2)*

Diagnostic Tool	Group 1		Group 2	
	Abnormal	Normal	Abnormal	Normal
DMSA scan	84 (67.7)	40 (32.3)	76 (88.4)	10 (11.6)
VCUG	40 (32.3)	84 (67.7)	43 (50)	43 (50)
US	40 (32.3)	84 (67.7)	43 (50)	43 (50)

*Values in parentheses are percents. UTI indicates urinary tract infection; DMSA, dimercaptosuccinic acid; VCUG, voiding cystourethrography; and US, ultrasonography.

Table 2. Results of DMSA Scan and VCUG in Patients with Definite Diagnosis of UTI (Group 1) and Those with Suspected UTI (Group 2)*

Groups	VCUG		Total
	Abnormal	Normal	
DMSA scan in Group 1 [†]			
Abnormal	39 (51.3)	37 (48.7)	76
Normal	4 (40)	6 (60)	10
Total	43 (50)	43 (50)	86
DMSA scan in Group 2 [‡]			
Abnormal	34 (40.5)	50 (59.5)	84
Normal	6 (15)	34 (85)	40
Total	40 (32.3)	84 (67.7)	124

*Values in parentheses are percents. UTI indicates urinary tract infection; DMSA, dimercaptosuccinic acid; and VCUG, voiding cystourethrography.

[†]*P* = .50.

[‡]*P* = .005.

Table 3. Grade of VUR in Patients with Suspected UTI (Group 2)*

VUR Grade	Unilateral Involvement		Bilateral Involvement	
	Right	Left	Right	Left
Mild (grades 1 and 2)	8 (53.3)	6 (50)	3 (23.1)	3 (23.1)
Moderate (grade 3)	6 (40)	6 (50)	9 (69.2)	8 (61.5)
Severe (grades 4 and 5)	1 (6.7)	0 (0)	1 (7.7)	2 (15.4)
Total	15	12	13	13

*Values in parentheses are percents. UTI indicates urinary tract infection and VUR, vesicoureteral reflux.

Table 4. Results of DMSA Scan and US in Patients with Definite Diagnosis of UTI (Group 1) and Those with Suspected UTI (Group 2)*

Groups	US		Total
	Abnormal	Normal	
DMSA scan in Group 1 [†]			
Abnormal	39 (51.3)	37 (48.7)	76
Normal	4 (40)	6 (60)	10
Total	43 (50)	43 (50)	86
DMSA scan in Group 2 [‡]			
Abnormal	34 (40.5)	50 (59.5)	84
Normal	6 (15)	34 (85)	40
Total	40 (32.3)	84 (67.7)	124

*Values in parentheses are percents. UTI indicates urinary tract infection; DMSA, dimercaptosuccinic acid; and US, ultrasonography.

[†]*P* = .50.

[‡]*P* = .005.

Table 5. Abnormal Findings on US in Patients with Suspected UTI (group 2)*

Findings	Patients
Mild hydronephrosis	11 (27.5)
Calculi	3 (7.5)
More than 2 cm difference in sizes of the kidneys	10 (25)
Increased echogeneity of the kidney parenchyma	8 (20)
Ectopic kidney	1 (2.5)
Doubled system	2 (5)
Increased thickness of the bladder [†]	5 (12.5)
total	40 (100)

*Values in parentheses are percents. UTI indicates urinary tract infection and US, ultrasonography.

[†]More than 2 mm with a full bladder and more than 5 mm with an empty bladder

The associations of the clinical and paraclinical findings with DMSA scan results are shown in Table 6. There were no association of DMSA scan results with fever, pyuria, hematuria, leukocytosis, erythrocyte sedimentation rate, and C-reactive protein.

DISCUSSION

In our study, the frequency of abnormal DMSA scan in children with a definite diagnosis of UTI was 88.4%, which agrees with most of the previous studies.^(9-11,13,16,19,20) In the children with a probable diagnosis of UTI (with abnormal findings on urinalysis and a negative culture), 67.7% had an

Table 6. Results of DMSA Scan in Association with Clinical and Paraclinical Findings in Patients with Suspected UTI (group 2)*

Findings	DMSA Scan			P
	Abnormal	Normal	Total	
Fever	47 (56)	20 (50)	67 (54.0)	.53
Pyuria	70 (83.3)	35 (87.5)	105 (86.7)	.54
Hematuria	47 (56)	23 (57.5)	70 (56.5)	.87
Peripheral blood leukocytosis	42 (50)	23 (57.5)	65 (52.4)	.43
ESR (more than 20 mm/h)	40 (47.6)	16 (40)	56 (45.2)	.42
CRP 2+	10 (11.9)	6 (15)	16 (12.9)	.63
CRP 3+	10 (11.9)	7 (17.5)	17 (13.7)	.39

*Values in parentheses are percents. DMSA indicates dimercaptosuccinic acid; ESR, erythrocyte sedimentation rate; and CRP, C-reactive protein.

abnormal DMSA scan. Also, fever was not present in nearly half of the patients with an abnormal DMSA scan which shows that there is no specific hallmark such as fever in patients with UTI.

Ultrasonography was not as accurate as ^{99m}Tc -DMSA renal scintigraphy for showing the pathologic changes in the kidney due to UTI; in our study, the US findings were abnormal in 40.5% and 51.3% of those with abnormal DMSA scan in groups 1 and 2, respectively. In other studies, the same results have been reported.^(19,20) In a study on 89 children with UTI, approximately 50% of normal kidneys on US showed either suspected or established scars on DMSA scan.⁽²⁰⁾ However, Morin and colleagues have reported better results by high-resolution US.⁽¹²⁾

In most studies,^(15,20-22) detection rate of VUR in UTI has been reported to be 30% to 50%. In our study, abnormal DMSA scan was associated with VUR. In group 2, VUR was present in one-third of the patients, and we could find VUR in 40.5% of the patients with an abnormal DMSA scan as a criterion of UTI diagnosis when the urine culture was negative. When UTI is accompanied by an abnormal finding on renal scintigraphy, it is a main risk factor of damaging the kidney parenchyma even without the existence of VUR^(13,15); therefore, using ^{99m}Tc -DMSA renal scintigraphy can be emphasized when the diagnosis of UTI is uncertain.^(3,13-15,18,20,22)

We found that VUR in the patients with abnormal DMSA scan was more frequent when the urine culture was positive for UTI. We reviewed the records of the patients to find out the probable cause of such a difference. Most of the patients in group 1 had recurrent pyelonephritis. This finding may be an explanation for the significant difference mentioned. Such a difference has also been demonstrated

in other studies.^(10,18) Nammalwar and colleagues studied 2 groups of children with pyelonephritis with positive and negative urine cultures. Of children with a positive urine culture, 92.9% had features of pyelonephritis on DMSA scan, of whom 82.1% had VUR, while in children with a negative urine culture and a positive DMSA scan, 65.4% had VUR.⁽¹⁸⁾ Levtchenko and coworkers evaluated the diagnosis of acute pyelonephritis with negative urine culture. Sixty percent of patients with clinical and scintigraphic evidence of pyelonephritis had VUR. This emphasizes the helpful role of renal scintigraphy for diagnosing VUR in the group of patients with pyelonephritis and negative urine culture.⁽¹⁰⁾ The rate of VUR is higher in the abovementioned study compared to our report which may be due to the selection of only febrile patients in these studies.

There are also some limited studies on renal scintigraphy in febrile children with unknown etiology. It has been shown that renal scintigraphy can reveal UTI in such cases.^(10,17,18)

CONCLUSION

Urinary tract infection is a very common disease in children and may be easily neglected. Renal scintigraphy using ^{99m}Tc -DMSA helps in the diagnosis of UTI in pediatric cases with unknown etiology. Our findings showed that an abnormal DMSA scan is a guidance to perform VCUG for the detection of VUR. According to our results, in children with a negative urine culture and abnormal urinalysis, US and DMSA scan help us decide whether to perform VCUG or not; VCUG is most probably negative for VUR if the results of US and DMSA scan are normal and enough evidence in favor of UTI lacks. In contrast, we recommend VCUG when DMSA

scan supports UTI despite a negative urine culture and a normal US.

CONFLICT OF INTEREST

None declared.

REFERENCES

- Rubenstein JN, Schaeffer AJ. Managing complicated urinary tract infections: the urologic view. *Infect Dis Clin North Am.* 2003;17:333-51.
- Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics.* 1999;103:843-52.
- Panaretto K, Craig J, Knight J, Howman-Giles R, Sureshkumar P, Roy L. Risk factors for recurrent urinary tract infection in preschool children. *J Paediatr Child Health.* 1999;35:454-9.
- Pylkkanen J, Vilks J, Koskimies O. Diagnostic value of symptoms and clean-voided urine specimen in childhood urinary tract infection. *Acta Paediatr Scand.* 1979;68:341-4.
- Bagga A, Babu K, Kanitkar M, Srivastava RN; Indian Pediatric Nephrology Group. Indian Academy of Pediatrics. Consensus statement on management of urinary tract infections. *Indian Pediatr.* 2001;38:1106-15.
- Hansson S, Brandstrom P, Jodal U, Larsson P. Low bacterial counts in infants with urinary tract infection. *J Pediatr.* 1998;132:180-2.
- Pead L, Maskell R. Study of urinary tract infection in children in one health district. *BMJ.* 1994;309:631-4.
- Ramage IJ, Chapman JP, Hollman AS, Elabassi M, McColl JH, Beattie TJ. Accuracy of clean-catch urine collection in infancy. *J Pediatr.* 1999;135:765-7.
- Biggi A, Dardanelli L, Pomero G, et al. Acute renal cortical scintigraphy in children with a first urinary tract infection. *Pediatr Nephrol.* 2001;16:733-8.
- Levtchenko EN, Lahy C, Levy J, Ham HR, Piepsz A. Role of Tc-99m DMSA scintigraphy in the diagnosis of culture negative pyelonephritis. *Pediatr Nephrol.* 2001;16:503-6.
- Biggi A, Dardanelli L, Cussino P, et al. Prognostic value of the acute DMSA scan in children with first urinary tract infection. *Pediatr Nephrol.* 2001;16:800-4.
- Morin D, Veyrac C, Kotzki PO, et al. Comparison of ultrasound and dimercaptosuccinic acid scintigraphy changes in acute pyelonephritis. *Pediatr Nephrol.* 1999;13:219-22.
- Camacho V, Estorch M, Fraga G, et al. DMSA study performed during febrile urinary tract infection: a predictor of patient outcome? *Eur J Nucl Med Mol Imaging.* 2004;31:862-6.
- Hansson S, Dhamey M, Sigstrom O, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. *J Urol.* 2004;172:1071-3.
- Moorthy I, Easty M, McHugh K, Ridout D, Biassoni L, Gordon I. The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. *Arch Dis Child.* 2005;90:733-6.
- Lin KY, Chiu NT, Chen MJ, et al. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. *Pediatr Nephrol.* 2003;18:362-5.
- Kao C, Hsieh J, Tsai S, et al. Using technetium-99m dimercaptosuccinic acid renal cortex scintigraphy to differentiate acute pyelonephritis from other causes of fever in patients with spinal cord injury. *Urology.* 2000;55:658-62.
- Nammalwar BR, Vijayakumar M, Sankar J, Ramnath B, Prahlad N. Evaluation of the use of DMSA in culture positive UTI and culture negative acute pyelonephritis. *Indian Pediatr.* 2005;42:691-6.
- Moorthy I, Wheat D, Gordon I. Ultrasonography in the evaluation of renal scarring using DMSA scan as the gold standard. *Pediatr Nephrol.* 2004;19:153-6.
- Bhatnagar V, Mitra DK, Agarwala S, et al. The role of DMSA scans in evaluation of the correlation between urinary tract infection, vesicoureteric reflux, and renal scarring. *Pediatr Surg Int.* 2002;18:128-34.
- Gordon I, Barkovics M, Pindoria S, Cole TJ, Woolf AS. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and meta-analysis. *J Am Soc Nephrol.* 2003;14:739-44.
- Mingin GC, Nguyen HT, Baskin LS, Harlan S. Abnormal dimercapto-succinic acid scans predict an increased risk of breakthrough infection in children with vesicoureteral reflux. *J Urol.* 2004;172:1075-7.

EDITORIAL COMMENT

The foremost merit of this paper is drawing attention toward an often neglected proportion of cases in which the indolent course of urinary tract infection, unaccompanied by constitutional symptoms, eludes aggressive treatment and follow-up. Having conveyed this message, one must bear in mind that a number of ambiguities in their study design preclude any further extrapolation from its data unless they are corroborated by more refined research.

Sterile pyuria in children, for instance, usually denotes sampling error or partial treatment rather than atypical infection, and therefore cannot be taken as a distinct entity. This is especially true since the history of previous UTI has not been recorded. This should have been formally assessed in the culture negative group.

Lack of a well defined group of normal controls can seriously flaw the significance of DMSA findings in group 2, particularly if the imaging was done in single-photon emission computed tomography

format, as apposed to the older pinhole scanning. Normal individuals, even without deceptive anatomical aberration of the kidney parenchyma, have been found to have abnormal DMSA scan in up to 35% of cases. An upper pole defect can even be expected to occur in 70% of the studied normal kidneys.⁽¹⁾ Practical recommendations must therefore await further study comparing the present findings with a normal group.

Pejman Shadpour

*Hasheminejad Kidney Center, Iran University
of Medical Sciences, Tehran, Iran*

REFERENCES

1. De Sadeleer C, Bossuyt A, Goes E, Piepsz A. Renal technetium-99m-DMSA SPECT in normal volunteers. *J Nucl Med.* 1996;37:1346-9.

REPLY BY AUTHOR

The authors would like to thank Dr Shadpour and acknowledge his comment. The following explanation may more elucidate the points mentioned.

It can be concluded from this study that in the children with the possibility of UTI, if pyuria has been repeated for several times and has been accompanied by abnormalities in the DMSA scan, cystography should be performed for detection of the VUR. Although this finding is often observed in the children, it may be neglected because of the obscure clinical findings. Therefore, the diagnosis of UTI is delayed and the disease is detected after some irreversible damage to the kidneys. Madani and colleagues reported that in Iran, the most common cause of the chronic kidney disease in children is

reflux nephropathy.⁽¹⁾ In this study, we tried to notify that recurrent pyuria can be a guide for the diagnosis of reflux due to the UTI with incomplete criteria. More studies in this regard are warranted.

Also, the normal variations in DMSA scan, including uptake reduction in the upper pole of the right kidney due to the compressive effect of the liver, have been considered by the authors. Overall, DMSA scan is a reliable diagnostic tool in the diagnosis of UTI and its sensitivity and specificity have been reported to be high.⁽²⁻⁵⁾

Ahmad Ali Nikibakhsh

*Department of Nephrology, Imam Khomeini
Hospital, Urmia University of Medical
Sciences, Urmia, Iran*

REFERENCES

1. Madani K, Otoukesh H, Rastegar A, Van Why S. Chronic renal failure in Iranian children. *Pediatr Nephrol.* 2001 Feb;16(2):140-4.
2. Lee BF, Chiou YY, Chuang CM, Wu PS, Wu YC, Chiu NT. Evolution of differential renal function after acute pyelonephritis. *Nucl Med Commun.* 2002 Oct;23(10):1005-8.
3. Moorthy I, Easty M, McHugh K, Ridout D, Biassoni L, Gordon I. The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. *Arch Dis Child.* 2005;90:733-6.
4. Kao C, Hsieh J, Tsai S, et al. Using technetium-99M dimercaptosuccinic acid renal cortex scintigraphy to differentiate acute pyelonephritis from other causes of fever in patients with spinal cord injury. *Urology.* 2000;55:658-62.
5. Nammalwar BR, Vijayakumar M, Sankar J, Ramnath B, Prahlad N. Evaluation of the use of DMSA in culture positive UTI and culture negative acute pyelonephritis. *Indian Pediatr.* 2005;42:691-6.