THE IMPORTANCE OF 99m-Tc DMSA RENAL SCINTIGRAPHY IN EVALUATION OF RENAL LESIONS IN CHILDREN WITH ACUTE PYELONEPHRITIS

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Abstract- Urinary tract infection (UTI) may lead to irreversible changes in renal parenchyma. Early diagnosis using scintigraphy with technetium-99m-labeled dimercaptosuccinic acid (DMSA) scan and early treatment may decrease or prevent development of renal parenchymal lesions. The aim of this study was to assess the occurrence of renal parenchymal lesion in children admitted with a first-time symptomatic UTI and to evaluate the relation between renal parenchymal damage and severity of vesicoureteral reflux (VUR). A total of 102 children with first time acute pyelonephritis (APN) were enrolled in the study. All children studied with DMSA scan and ultrasonography (US). Voiding cystourethrography (VCUG) was performed in 98 children when urine culture became negative. Changes on the DMSA scan and US were found in 178 (88%) and 5 (2.4%) out of 203 renal units during the acute phase, respectively. All abnormal renal units on US showed severe parenchymal involvement on DMSA. We also found significant correlation between severity of VUR and abnormal US results on kidneys. Of 40 kidneys with reflux, 38 (95%) were found to have abnormal renal scan. Among 155 kidneys with non-refluxing ureters 132 (85.2%) revealed parenchymal changes on renal cortical scintigraphy. Kidneys with moderate to severe reflux were more likely to have severe renal involvement. We found a high incidence of renal parenchymal changes in children with APN. Additionally, renal involvement was significantly higher in children with moderate to severe reflux. When there are high-grade VUR and female gender, the risk of renal parenchymal involvement is higher.

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INTRODUCTION

The diagnosis of urinary tract infection (UTI) in children is based on significant bacteriuria. The level of infection (*i.e.*, whether the infection involves the kidneys or only the lower urinary tract) is of great importance for the choice of treatment and prognosis. The children with renal involvement are at risk of permanent renal damage, which may lead to hypertension, proteinuria, hyposthenuria, complications during pregnancy, and even renal failure (1). Because the clinical symptoms are nonspecific, the diagnosis of renal infection needs to be supported by laboratory data and radiologic imaging. Renal cortical scintigraphy with technetium-99m-labeled dimercaptosuccinic acid (DMSA), although not perfect, appears to be the best clinically applicable standard of reference for the diagnosis of acute pyelonephritis (APN) (2-4). It is

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considered the most sensitive technique for the identification of the renal parenchymal change in APN, as well as in the detection of scarring. Acute DMSA renal scan defects persisted as renal scarring in 36–52% of kidneys (5). Some controversy exists about the usefulness of acute renal scintigraphy. Many pediatric nephrologists share the view that the diagnosis of complicated UTI is based on clinical and biological data, and that renal cortical scintigraphy is generally not necessary for the diagnosis (6, 7). The aim of this prospective study was to assess the occurrence of renal parenchymal lesion in children admitted with a first episode of symptomatic UTI and to assess the relation between renal parenchymal damage and severity of vesicoureteral reflux (VUR).

MATERIALS AND METHODS

One hundred-two patients (9 boys, 93 girls) aged 1 month to 12 years (mean 2.85 ± 2.92 years) were included in the study from November 2005 to March 2007. The study was approved by Ethics Committee of Tehran University of Medical Sciences and written informed consent was obtained from parents of all subjects.

All children admitted to hospital because of high suspicion of APN, defined as follows: fever, with a temperature 38.5 C°, erythrocyte sedimentation rate (ESR) > 20 mm/hr or increased C-reactive protein (CRP), alterations in the urinary sediment (leukocyturia, bacteriuria, hematuria) and a positive urine culture result (growth of single organism with colony counts equal to or greater than 10^5 colony-forming units/ml). Samples were collected as clean-voided midstream urine. Only those with proven UTI were included in the study. The patients were divided into three groups, those under 1 year of age (n = 34), those between 1 to 5 (n = 51) and children over 5 years old (n = 17).

Two hundred three kidneys were investigated by DMSA scan and renal ultrasound within the first days after admission. Images were obtained by means of a gamma equipped with a high-resolution collimator after an intravenous injection of DMSA scintigraphy, according to a standard schedule (8). About 3–4 hours after injection with the tracer, one posterior, one anterior and two posterior oblique images of the kidneys were acquired, with the patient prone below the camera. The fractional left and right renal activity was calculated for each kidney. The renal scintigraphic patterns were independently interpreted by two senior nuclear-medicine physicians, and the criteria used for the interpretation of the images did not change during the period of the investigation. A kidney with regular shape and a tracer uptake that appeared to be homogenous was considered as normal. Single or multiple cortical defects, focal or diffuse photopenic patterns in one kidney were considered as abnormal (9, 10). The scan was considered to be abnormal for an old lesion (scar) when one or more areas of focal decreased uptake associated with contraction and loss of volume in the involved cortex were noted (6).

Patients with previous history of UTI, structural abnormalities such as neurogenic bladder, posterior urethral valves, ureteroceles or other congenital anomalies were excluded from the analysis. A kidney uptake of 45–55% of the total renal activity was considered as normal (symmetrical renal split function). The involvement of each kidney was visually graded as mild (focal defect in uptake), moderate (uptake of renal radionuclide of 20-40%) and severe (shrunken kidney with uptake less than 20%) (11). All scintigrams were independently assessed by two experienced radiologist who used standard criteria previously defined by Patel *et al.* (12). Renal ultrasound was performed on computerized sonographic units equipped with 3.5 MHz and 5.0 MHz transducers.

The renal sonograms were interpreted by a pediatric radiologist without the knowledge of the findings from DMSA scans. The criteria of renal abnormality were: focal or generalized hyperechogenicity or hypoechogenicity, increase in renal size, loss of corticomedullary differentiation, thickened pelvic wall, irregular outlining of the kidney and parenchymal reduction. For all patients a voiding cystourethrography (VCUG) was done early in the course of the illness, generally within 5–7 days of hospitalization and always before the patient was discharged from the hospital (13). The radiographic cystograms were evaluated for the presence and grade of reflux using the international

grading system (14). Patients were treated for 14 days with an antibiotic chosen according to bacterial susceptibility tests. No patient was excluded from the analysis during the hospital stay.

The chi-squared procedure and the Fisher exact test were used to determine the statistical significance of the relationships between variables. A *P* value below 0.05 was considered statistically significant.

RESULTS

One hundred-two patients (9 boys, 93 girls) aged 1 month–12 years (mean 2.85 ± 2.92 years) with a first documented UTI were included in the study between November 2005 to March 2007.

The median time between the diagnosis of UTI and cortical scintigraphy was 1.5 days (range: 1-3 days). Of the 102 children with a first documented pyelonephritis, 178 out of 203 (87.7%) renal units (1 patient had single kidney) were abnormal on scintigraphy during the acute phase (28.1% in children younger than 1 year, 46.3% in those between 1 to 5 and 13.3% in children older than 5 years). The extent of changes in DMSA scan was mild in 113/178 kidneys (63.5%), moderate in 40/178 kidneys (22.5%) and severe in 25/178 kidneys (14%). Of the 178 renal units with abnormal scintigraphy ultrasound findings were abnormal only in 5 kidneys. All abnormal renal units on ultrasonography (US) had severe parenchymal involvement on DMSA. US was normal in all renal units with normal DMSA scintigraphy findings. The authors also found the correlation between severity of VUR and abnormal US results on kidneys (P = 0.002, r =0.22).

Topographic analysis of the 178 focal lesions showed that 49.8% were localized to the upper poles, 12.2% to the middle third, and 38% to the lower poles of the kidneys. Ninety eight out of 102 children underwent VCUG. Reflux was documented in 40/195 kidneys (20.5%). Table 1 shows VCUG findings according to number of patients and renal units, respectively.

Table 1. Voiding cystourethrography findings according to number of patients and renal units

	Patients		Renal units	
Reflux	**No.**	**%**	**No.**	**%**
None	64	65.3	155	79.4
Grade				
I–II	10	10.2	19	9.8
III	19	19.4	15	7.7
IV–V	5	5.1	6	3.1
Total	98	100	195	100

The degree of reflux was mild (grades I and II) in 19/40 kidneys (47.5%), moderate (grade III) in 15/40 kidneys (37.5%) and severe (grades IV and V) in 6/40 kidneys (15%). As shown in Table 2, the frequency of renal parenchymal abnormalities in the presence of VUR and in non-refluxing renal units was similar (85.2% vs 95%, $P > 0.05$). Kidneys with moderate to severe reflux were more likely to have severe renal involvement (P = 0.001). Girls were more prone to developing APN than boys (P = 0.04).

Parenchymal abnormalities on scintigraphy were associated with mild reflux in 18/40 (45%) and moderate to severe reflux in 32/40(80%) of renal units, respectively ($P < 0.001$, r = 0.23).

DISCUSSION

UTI is common in children. About 1-2% of boys and 3-7% of girls experience at least one episode of UTI before the age of 11 years (15, 16).

Table 2. DMSA scintigraphy and voiding cystourethrography findings*

	Normal DMSA		Abnormal DMSA		Total	
Renal units	**No.**	**%**	**No.**	**%**	**No.**	**%**
Without reflux	23	14.8	132	85.2	155	100
With reflux	2	5	38	95	40	100
Total	25		170		195	

Abbreviations: DMSA, dimercaptosuccinic acid.
*$P > 0.05$.

The ultimate goal of treatment for pyelonephritis in children is prevention or reducing the morbidity and long-term clinical sequelae of renal scarring, including arterial hypertension, hyposthenuria, proteinuria and chronic renal failure (17-20).
Experimental investigations have shown that inflammation has an important role in the pathogenesis of renal damage in pyelonephritis, which involves the local infiltration of polymorphonuclear leukocyte and the extracellular release of cytotoxic metabolites (21-23). DMSA scintigraphy is currently considered the imaging agent of choice for estimating the presence and extension of acute parenchymal changes as well as the development of permanent renal scarring. It has been compared with histopathologic findings, and there has been 97% agreement between them (24). DMSA uptake reflects renal tubular cell function and is therefore affected by both intrarenal blood flow and proximal tubular cell membrane transport (25). It is well known that DMSA scintigraphy reflects the function of proximal tubular cells and the intrarenal blood flow (25, 26); consequently, an infection limited to the papilla and the medulla may not be clarified on a DMSA renal scan. This study revealed a high frequency of acute inflammatory changes on DMSA scan in 87.6% of renal units, although the clinical and biological criteria were compatible with APN. This is similar to the findings reported by others (27-30).

These data emphasize the fact that children with first-time febrile UTI are at risk for acute inflammatory renal parenchymal damage. VUR is a known risk factor for renal scarring. It has been found in up to 88% of children with DMSA scans during febrile UTI (6, 13, 27). In our experience, VUR was found in 38/40 kidneys (95%) with evidence of pyelonephritis on DMSA scan. VUR was absent also in 132/155 kidneys (85.2%) with renal parenchymal involvement, which emphasizes that abnormalities at DMSA scan commonly occur in the absence of reflux (13, 31, 32)

Our findings agree with the observations of other investigators. In the study of Biggi *et al.* (6) VUR was present in 27% of the renal units with evidence of acute pyelonephritis on DMSA renal scan and absent in 47**%.** Majd found VUR in 37% of children with evidence of acute pyelonephritis on DMSA (13).

In the study of Benador *et al.*, VUR was present in 39% and absent in 61% of children with evidence of acute pyelonephritis (33). Thus, our results confirm that a high percentage of febrile UTI, as documented by acute DMSA renal scan, can occur without the presence of a VUR.

In this series the incidence of abnormal findings on DMSA was significantly higher in children with moderate to severe reflux. These results are in accordance with the high percentage renal abnormalities that recently reported by Preda *et al.* (34).

Camacho *et al.* found that children with abnormal DMSA have a higher frequency of VUR than children with normal DMSA (48% vs 12%) (35). In or previous report reflux was present in 28.5% of normal kidneys without any abnormality (32). In present study of 25 renal unit with normal DMSA only 2 (8%) had VUR (grade I or II) and of 170 renal unit with abnormal DMSA 40 (23.5%) had VUR. Our results show lower frequency of VUR in children with normal DMSA than reported by our group and others (6, 13, 32, 35**).** These data emphasize the fact that children with normal renal scintigraphy during acute UTI have a low risk of renal damage. However, the incidence of the abnormal findings was significantly higher when the grade of VUR was higher. In 80% of renal units with abnormal DMSA scans the grade of reflux was moderate to severe. Girls were more prone to developing APN than boys. This finding was in agree with results as reported by Zaki *et al.* (36).

One theory for VUR as a cause of pyelonephritis concerns the elective localization of scars in the polar regions of the kidney (37, 38). In the present study, the frequency of acute renal changes was higher in upper and lower poles of the kidneys, whether there was a reflux or not. In contrast to findings by Biggi *et al.* (39), these data are in accordance with the high percentage of polar abnormalities that found in our previous study and others (33, 40).

US was abnormal in 5 renal units compared with 170 with abnormal DMSA findings, while no positive US examination was found in patients with

normal DMSA. This confirms that US examination is not an adequate diagnostic method (41, 42). In conclusion, we found a high incidence of renal parenchymal changes in children with APN. Additionally, renal involvement was significantly higher in children with moderate to severe reflux. When there are high-grade VUR and female gender, the risk of renal parenchymal involvement is higher.

Conflict of interests

We have no competing interests.

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