Original article

Acute phase 99mTc-dimercaptosuccinic acid scan in infants with first episode of febrile urinary tract infection

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Background: **99mTc-dimercaptosuccinic acid (DMSA) scan is the golden standard for the diagnosis of acute pyelonephritis and renal scaring. We investigated the use of acute phase DMSA scan in infants presented promptly to the hospital because of the first episode of their febrile urinary tract infection (UTI).**

Methods: **Ninety-eight infants with microbiologically confirmed first episode of febrile UTI were studied. DMSA scans were carried out within 7 days in these infants after admission. Infants with an abnormal acute DMSA scan underwent a second DMSA scan 6-12 months later.**

Results: **Overall, acute DMSA scan was abnormal in 16 (16.3%) of the 98 patients. There were no differences in sex, age, fever over 38.5°C, blood inflammation indices, or evidence of vesicoureteral reflux (VUR) between patients with normal and abnormal acute DMSA scan ($P>0.05$). However, infants with grade III to V VUR as well as those with delayed treatment presented significantly increased renal involvement by acute DMSA scan ($P<0.05$). The sensitivity and specificity of abnormal acute DMSA scan to predict grade III to V VUR were 50% and 88% respectively. Its positive and negative likelihood ratios were 4.16 and 0.57, respectively. Of 16 children with abnormal initial DMSA scan results, 14 underwent a second DMSA scan. Follow-up DMSA scans were normal in 12 of the 14 children.**

Conclusions: **Parenchymal damage found in a minority of infants with febrile UTI presented promptly to the hospital. Acute phase DMSA scan should be carried out only in selected patients. An abnormal acute DMSA scan is a moderate predictor for dilated VUR and its ability to exclude VUR is restricted.**

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Key words: **99mTc-dimercaptosuccinic acid; infants; pyelonephritis; vesicoureteral reflux; urinary tract infection**

Introduction

Urinary tract infection (UTI) is the most common bacterial infection in infants and young children.[1] It may be limited to the lower urinary tract or may involve the renal parenchyma. In the latter cases, it leads to renal cortical scars that increase the risk of subsequent hypertension and renal insufficiency.[1,2] Reported risk factors for the development of renal cortical scars include the presence of vesicoureteral reflux (VUR), mainly high grade, young age, delayed initiation of antimicrobial treatment, and recurrent infections.[2,3] Recent reports have re-evaluated the role of the above mentioned factors in scar formation.[3-5]

Renal scintigraphy using 99m-Technetium-dimercaptosuccinic acid (mTc-DMSA) is the accepted reference standard for detecting renal involvement including febrile UTI and renal sequels as scarring later.[6] However, in the absence of adequate data, there is conflicting advice in the literature over the timing of renal cortical scintigraphy. Whether acute and follow-up DMSA scans or both scans should be performed remains open to discussion.[7-9]

The present study was undertaken to detect pyelonephritic changes by acute phase DMSA scan and renal scaring by follow-up DMSA scan in infants younger than 1 year old who were admitted to the hospital for the first episode of UTI. The utility and

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significance of DMSA were evaluated in the selected infants.

Methods

Study population

Ninety-eight infants consecutively admitted to our department with microbiologically confirmed first episode of febrile UTI were prospectively studied. The infants should be 1 to 12 months of age, with no earlier UTI or evidence of obstructive nephropathy in prenatal screening or other urogenital abnormalities. The infants were treated with antibiotics immediately after their urine and blood samples were collected. They were treated empirically with antimicrobial agents (amoxicillin + clavulanic acid, 2nd or 3rd generation cephalosporins) until organisms were identified and antimicrobial drug susceptibility was known. Treatment with antibiotics continued intravenously until the infants presented afebrile for 24 to 36 hours. A 10- to 14-day course of oral antibiotics was provided. The time between the onset of fever and the start of therapy was recorded. Infants with dilated VUR (grades III to V) shown by cyclic voiding cystourethrography received prophylactic therapy with trimethoprime-sulfomethoxazole or 2nd generation cephalosporin.

Measurements

Laboratory tests for all infants with suspected UTI involved white blood cell count (WBC) and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), routine biochemical tests, urinalysis, and urine culture by suprapubic paracentesis or catheterization. The growth of any number of colonies and $>10^4$ colony-forming units/mL was considered as a positive urine culture. Ultrasound examination was carried out to detect urinary tract obstruction or other gross deviations of the urinary tract within the 1st and 3rd day of admission. DMSA scan was routinely performed within the 2nd and 7th day after initiation of treatment (acute phase DMSA) to identify patients with acute pyelonephritis. Pyelonephritis was defined by the presence of focal or diffuse areas of decreased radionuclide uptake on DMSA scan, with preservation of the normal outline of the kidney.[10] Infants with abnormal acute phase DMSA scans underwent another scan 6-12 months later. An abnormal second scan was defined by the presence of decreased uptake of DMSA associated with loss of the contour of the kidney or by the presence of cortical thinning. A kidney with a differential function of ≤44% was considered abnormal.[10] A voiding cystourethrography for detection of VUR was performed in all infants. The enrollment of infants into the study was approved by the Ethical Committee of Hippokration Hospital.

Statistical analysis

Fisher's Exact test was used to compare the proportion of abnormal initial DMSA in different groups of the infants. Mean blood absolute neutrophil count, ESR, CRP and median duration of fever before initiation of treatment in the normal DMSA group were compared with those in the abnormal DMSA group by using the Mann-Whitney *U* test. The ability of acute phase DMSA scan to detect VUR was based on sensitivity, specificity, positive prognostic value (PPV), negative prognostic value (NPV), and positive and negative likelihood ratio. A P value <0.05 was considered statistically significant.

Results

Totally 98 infants (57 boys and 41 girls) aged 1 to 12 months (median: 4.2 months) with first episode of febrile UTI and no obstructive nephropathy were enrolled in this prospective study. All infants completed the initial imaging with renal ultrasound, acute DMSA and voiding cystourethrograpy. Two infants missed the follow-up DMSA scan. Of the 98 patients, 59 (60.2%) were infants ≤3 months old. *Escherichia coli* was isolated from the urine of 82 (83.6%) infants, *Klebsiella* pneumonia from 5 (5.1%), *Pseudomonada aureginosa* from 7 (7.1%), *Enterobacter* from 2 (2.0%), and *Proteus* from 2 (2.0%). No correlation between any type of bacteria and renal involvement was documented (P=0.380).

The median time between the onset of symptoms and the start of therapy was 36 hours (range: 12 hours to 6 days). The median time between the start of

Table 1. Epidemiologic and clinical characteristics of patients in relation to acute DMSA scan findings

Variables	Normal acute DMSA scan (%)	Abnormal acute DMSA scan (%)	*P*
Sex			
Male	51 (62.2)	6 (37.5)	NS
Female	31 (37.8)	10 (62.5)	
Age			
≤3 mon	52 (63.4)	8 (50.0)	NS
>3 mon	30 (36.6)	8 (50.0)	
Fever			
38-38.5°C	44 (53.6)	6 (37.5)	NS
>38.5°C	38 (46.4)	10 (62.5)	
Duration of fever			
≤3 d	73 (89.0)	9 (56.3)	0.010
>3 d	9 (11.0)	7 (43.7)	

DMSA: 99mTc-dimercaptosuccinic acid; NS: no significance.

Table 2. Laboratory and imaging findings of patients in relation to acute DMSA scan findings

Variables	Normal acute DMSA scan (%)	Abnormal acute DMSA scan (%)	*P*
White blood cell counts			
≤15 000/mm^3	43 (52.5)	10 (62.5)	NS
>15 000/mm^3	39 (47.5)	6 (37.5)	
CRP			
≤20 mg/L	44 (53.6)	6 (37.5)	NS
>20 mg/L	38 (46.4)	10 (62.5)	
ESR			
≤20 mm/h	40 (48.7)	5 (31.2)	NS
>20 mm/h	42 (51.3)	11 (68.8)	
MCU			
No VUR	57 (69.5)	8 (50.0)	NS
VUR	25 (30.5)	8 (50.0)	
Grades I, II	19 (76.0)	2 (25.0)	0.008
Grades III, IV, V	6 (24.0)	6 (75.0)	

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MCU: micturating cystourethrography; VUR: vesicoureteral reflux; NS: no significance.

treatment and acute phase DMSA scan was 3.27 days (range: 2-7 days). Fever over 38.5°C was measured in 48 infants (48.9%).

Acute phase DMSA scan revealed renal changes in 16 (16.3%) of the 98 infants. There were no differences in sex, age and fever over 38.5°C between infants with normal and abnormal acute DMSA scans (Table 1). However, the percentage of abnormal acute phase DMSA scans was significantly higher as patients received antibiotic therapy on the third day after appearance of fever (P=0.010). Leukocytosis, ESR, CRP and VUR were compared in patients with normal and abnormal acute phase DMSA scans and no significant difference was identified (Table 2). Voiding cystourethrography identified VUR in 33 infants (34%), 19 males and 14 females. Among these infants, 21 had grade I-II VUR and 12 had grade III-V VUR.

Infants with grade III-V VUR had a significantly increased renal involvement shown by acute DMSA scans compared to those with grade I-II VUR (P=0.008). The sensitivity and specificity of abnormal acute DMSA scintigraphic results to predict grade ≥III VUR were 50% and 88%, respectively. The PPV and NPV were 37.5% and 92.5%, respectively and the positive, and the negative likelihood ratios were 4.16 and 0.57, respectively. Of 16 infants with abnormal initial DMSA scan, 14 underwent a second DMSA scan 6-12 months after infection. No patients with renal changes on acute-phase DMSA scan had recurrence of UTI in the second year. The follow-up DMSA scan was normal in 12 (75.0%) of the 14 infants. One infant with chronic renal cortical scarring shown by the follow-up DMSA scan had grade V VUR.

Discussion

UTIs in children are a major cause of morbidity.[11] Clinical features of acute pyelonephritis are often nonspecific and misleading in pediatric patients, especially in neonates and infants.[12,13] Recognition of renal parenchymal involvement is thus extremely important. DMSA scan is useful for detecting renal inflammation caused by pyelonephritis.[14] Whether single acute DMSA scan and follow-up or both should be performed remains controversial. In addition, whether DMSA study in the acute period of febrile UTI is useful for assessment of prognosis and outcome in patients is unclear.

The present study assessed renal findings of acute-phase DMSA scan in young children with the first episode of UTI. Specifically, abnormal initial DMSA scan was seen at the first episode of UTI in 16.3% of infants of less than 1 year old. Several studies on acute pyelonephritis by DMSA scan revealed that 50%-90% of infants with febrile UTI had abnormal DMSA renal scans.[14-17]

The lower percentage of acute phase DMSA scans in the present study could be attributed to young age of the infants, i.e., most of them were younger than 3 months. Immature tubular function in infants aged 2 to 3 months may be responsible for the low rate of DMSA scans in this age group.[18] Moreover, there is a lower risk of renal damage in children of less than 1-2 years old who have a first febrile UTI.[19] This might be due to early treatment of our infants and the different criteria for admission.

Delayed treatment in agreement with our findings has been considered as an important clinical factor for renal damage.[7,20-22] Uptake defects in acute infection are recorded only when the treatment is delayed for 48 hours.[23]

Our study showed abnormal acute DMSA scan in infants with or without VUR but there was no significant difference. This finding suggests that abnormalities of DMSA scan, which are consistent with pyelonephritis, appear in the absence of VUR. Therefore, reflux is involved in the pathogenesis of pyelonephritis, such as bacterial virulence factors and host susceptibility. In our study, infants with grade III-V VUR presented increased renal involvement shown by acute DMSA scans compared to those with grade I and II VUR. This finding is in agreement with that DMSA scan is abnormal mostly in infants with dilated VUR.[24-27] Furthermore, abnormal acute DMSA presented a low sensitivity and NPV for detecting dilated VUR.[27] Hansson et al[24] found a higher NPV of 95.2%, but there was a low negative likelihood ratio of 0.37, similar to 0.5 of our study. Thus there is

a restricted ability of acute DMSA scan for detecting dilated VUR. Others found high sensitivity and NPV of acute DMSA scan, suggesting that normal DMSA scan makes cystourethrography unnecessary in examination of infants with UTI.[25,26] The increased sensitivity in these studies could attribute to the earlier performance of acute DMSA scan and the differences in study populations.

Hoberman et al[28] examined 309 children with UTI by DMSA scan in the acute period and a follow-up study of 6 months. The follow-up study showed renal parenchymal involvement in 9.5% of the children. Another study showed similar results that 9.8% of children with renal scars shown by follow-up DMSA scan.[29] In our study, follow-up DMSA scan was normal in 12 of the 14 infants. One of 2 infants with scars shown by follow-up DMSA scan had grade V VUR. Renal scarring was found to be closely related to delayed diagnosis and inappropriate treatment of acute pyelonephritis.[20-22,30] The median interval between the onset of symptoms and the start of therapy was 36 hours in our patients. Moreover, the prevalence of renal scars after treatment of acute pyelonephritis may be over-estimated by researchers performing renal cortical scintigraphy. In our patients, follow-up DMSA scan was performed at least 6 months after the episode of UTI. While DMSA scan is the gold standard for identification of renal damage, it cannot differentiate congenital from acquired renal scars. Renal damage may be congenital, especially in infants with grade V VUR, representing mostly a dysplastic kidney and less a postpyelonephritic acquired damage.[31]

In conclusion, the presence of parenchymal damage in only 16% of young children with first episode of febrile UTI who are promptly admitted to the hospital and have good long-term outcome suggests that acute phase DMSA scan may not be necessary. Abnormal acute phase DMSA scan is related to delayed treatment. Moreover, abnormal acute DMSA scan is only a moderate predictor for dilated VUR, and its ability to exclude VUR is restricted.

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