

Predictors of abnormal renal cortical scintigraphy in children with first urinary tract infection: the importance of time factor

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Abstract

Introduction We evaluated different factors predicting the development of acute pyelonephritis in Iranian children, with special attention to time factor. **Methods** One hundred nineteen patients (93 females and 26 males; age = 32.6 ± 30.8 months) with first urinary tract infection (UTI) were evaluated. None had previous urological problems. Prior to antibiotic therapy blood samples were gathered for laboratory evaluation. Vital signs on admission were measured. Clinical and laboratory indices, including therapeutic delay time (TDT) and therapeutic response time (TRT), were measured. Most patients were evaluated with renal ultrasound in the first three days following admission. All patients underwent dimercaptosuccinic

acid (DMSA) renal scintigraphy and 71 were assessed for vesicoureteral reflux (VUR).

Results DMSA scans were abnormal in 77 cases, of which 11 cases had bilateral renal involvement. Mean values for TDT, TRT, leukocyte count (LC), absolute neutrophil count (ANC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were 74.1 h, 39.6 h, $15725 \pm 6682 \text{ mm}^{-3}$, $10772 \pm 6458 \text{ mm}^{-3}$, $51.9 \pm 32.5 \text{ mm}$, and $27.3 \pm 25.1 \text{ mg l}^{-1}$, respectively. VUR was present in 29 of 142 evaluated renal units.

Conclusion $\text{TDT} \geq 48 \text{ h}$, $\text{TRT} \geq 24 \text{ h}$, axillary temperature $\geq 39^\circ\text{C}$, $\text{LC} \geq 13500 \text{ mm}^{-3}$, and age ≥ 18 months predicted abnormal DMSA scan in patients with first episode of UTI. Considerably higher TDT and TRT values of the current study compared to previous ones suggests the more important role of time factor in predicting abnormal DMSA findings in a developing country than in developed ones.

Keywords Acute pyelonephritis · DMSA · Renal scar · Scintigraphy · Urinary tract infection

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Introduction

Urinary tract infections (UTI) are among the most prevalent infections in the pediatric population. Various conventional clinical and laboratory indices

are used to differentiate simple lower UTI from the involvement of renal parenchyma during urinary infection. Newer laboratory markers are also actively investigated for such distinction with variable results [1, 2]. As none of these indices are perfect, ^{99m}Tc -dimercaptosuccinic acid (^{99m}Tc -DMSA) is often used for this reason [3, 4].

There is always some delay in referring a child with UTI to medical attention. This time period varies in different populations, possibly due to different cultural, social and financial factors, as well as availability of medical care facilities. As the delay time from the onset of the disease until the commencement of appropriate antibiotic treatment ultimately affects renal involvement [5, 6], this factor should be included in the decision-making process. Previous studies [5, 7–9] have evaluated the effect of the time factor in several clinical centers, all in developed countries. As the socio-sanitary environment may be different in developing countries (e.g., more delay in bringing a sick child to medical attention), the time factor may have a more pronounced influence on the development of acute renal damage during UTI in such circumstances.

The goal of this study was to evaluate several factors (including time) which may predict the presence of abnormal DMSA scintigraphic findings in an Iranian pediatric population with first episode of UTI.

Methods

Study population

This is a prospective study performed on 119 consecutive children (93 females and 26 males) with their first episode of UTI. To include patients in the study patients should have normal prenatal sonography, excluding any structural uropathy or urological problems. Patients with history of any urological abnormality, previous episode of UTI, antibiotic treatment for the current urinary tract infection, or patients whose urine culture failed to become positive were excluded from the study. The study was approved by the ethics committee of Tehran University of Medical Sciences and all patients and their parents gave their informed consent before entering in to the study.

Laboratory test

Presence of UTI was confirmed by significant bacteriuria in single urine culture obtained by suprapubic vesical puncture or urinary bladder catheterization. Significant bacteriuria was defined as $>10^4$ cfu ml⁻¹ on a catheterized specimen and any number of bacteria in a suprapubic aspirate. Before empirical antibiotic administration, blood samples were drawn to determine leukocyte count (LC), absolute neutrophil count (ANC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Vital signs including axillary temperature were obtained at the time of emergency ward admission.

Time parameter definitions

The children's mothers or their direct caregivers were asked about two clinical variables. The first one was the therapeutic delay time (TDT), defined as the hours passed since the onset of fever until the first dose of adequate antibiotic administration, while the second variable was the therapeutic response time (TRT), defined as the number of hours from the administration of the first dose of adequate antibiotic until the resolution of fever ($\leq 37.5^\circ\text{C}$), when the patient was off antipyretics.

Diagnostic imaging

Renal ultrasonography was performed in most patients (105/119) within the first three days of their admission to the hospital. All patients underwent ^{99m}Tc -DMSA renal scintigraphy within one week of their hospital admission. The activity for injection of ^{99m}Tc -DMSA (AEOI, Tehran, Iran) was calculated using a body surface area scaling factor on the adult dose activity of 5 mCi (185 MBq) [10]. Two and half hours following injection, anterior, posterior and posterior oblique images of both kidneys were acquired using a single-head gamma camera (model DSX; Summit Medical Vision, France) fitted with a low-energy, parallel-hole, high-resolution collimator. A zoom factor of 1.33 to 2 was used. Images were obtained with 500 kcounts for each view using a 256×256 matrix. ^{99m}Tc -DMSA renal scintigraphies were interpreted by three separate nuclear physicians, well-experienced in pediatric nuclear medicine, who were all blinded to each other's interpretations

as well as to patients' history. If there was any inconsistency between the interpreters, the final decision was made by consensus. Seventy one patients underwent voiding cystourethrography (VCUG) approximately 4 weeks after admission in an outpatient unit after confirming the resolution of the UTI by a negative urine culture. The presence of vesicoureteral reflux (VUR) was classified into five grades, according to the guidelines of the International Reflux Study in Children [4, 11]. VUR was defined as mild (grades I and II), moderate (grade III) or severe (grades IV and V).

Statistical analysis

Data were expressed as mean values \pm standard deviation (SD) and maximum and minimum values. Sensitivity (S), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), and risk ratio were used for the assessment of various diagnostic tests and variables. For calculation of the cut-off values at which different diagnostic tests or clinical factors (ESR, CRP, body temperature, ANC, LC, TDT, and TRT) can predict the presence of ^{99m}Tc -DMSA lesions, receiver operating characteristic (ROC) curves were drawn. The area under the curve of each diagnostic test or clinical factor represents the probability that the value of that test or factor for a randomly chosen case of abnormal DMSA renal scan will be more than the value of a randomly chosen normal case (with normal DMSA scan). Comparisons of two mean values were performed using a paired *t*-test and a non-paired *t*-test where appropriate. Statistical multi-group comparisons were performed with ANOVA followed by Tukey multiple comparison tests with correction. For univariate analysis, qualitative and categorical variables were analyzed using the Pearson χ^2 -test. Variables that were statistically significant in the univariate analysis entered the multivariate analysis using the backward logistic regression stepwise method. The significance levels for entering and removing an independent variable were set at 0.05 and 0.10, respectively. As the prevalence of the pyelonephritis in our population was higher than 10%, OR could not be considered a good estimate of the risk ratio [10]. Thus, OR was adjusted for the prevalence of pyelonephritis in our population giving rise to risk ratio which now could be regarded as a

better predictor of the patient outcome. All statistical analyses were performed using SPSS 11.5 for Windows software. Statistical significance was set as a *P* value of ≤ 0.05 .

Results

One hundred nineteen patients entered the study from June 2006 till December 2007, of which 93 cases were female (78.2%) and 26 were male (21.8%) with mean age of 32.6 ± 30.8 months (range 1.0–120 months). The median age at the time of diagnosis was 7.5 months (range 1.0–107) for boys and 23.0 months (range 2.0–120) for girls.

Mean TDT was 74.1 h (range 6.0–240), while mean TRT was 39.6 h (range 4–120). *Escherichia coli* was the most frequent pathogen (101 cases, 84.9%). *Klebsiella* in 8 cases (6.7%), *Enterobacter* in 7 cases (5.9%) and *Proteus* and *Pseudomonas* in the remaining 3 (2.5%) were the least frequent pathogens.

A whole blood cell count was done for all (119) children, while first hour ESR and CRP were performed in 117 and 64 children, respectively. Mean values \pm SD of the LC, ANC, ESR, and CRP were $15725 \pm 6682 \text{ mm}^{-3}$, $10772 \pm 6458 \text{ mm}^{-3}$, $51.9 \pm 32.5 \text{ mm}$, and $27.3 \pm 25.1 \text{ mg l}^{-1}$, respectively.

^{99m}Tc -DMSA scan was normal in 42 patients. Unilateral scintigraphic abnormalities were seen in 66 patients and, in the remaining 11 patients, bilateral renal involvement was noted. Renal ultrasonography was performed in 105 patients, where pyelonephritic changes were suggested only in 18 cases. Hence, the sensitivity, specificity, PPV and NPV of the ultrasonography in the diagnosis of pyelonephritis (using DMSA scan as the gold standard) were 26.6, 97.5, 94.4, and 45.9%, respectively.

VCUG was performed in 71 cases (142 renal units). VUR was noted in 22 patients (30.9%) and 29 renal units (20.4%). VUR was mild in 13 renal units (9.2%), while it was moderate and severe in 11 (7.7%) and 5 (3.5%) renal units, respectively. Bilateral VUR was present in 7/71 (9.8%) of patients. Among 22 patients who had unilateral or bilateral VUR, 6 had normal DMSA renal scan and 16 had abnormal findings, while for 49 patients who had no VUR these figures were 22 and 27, respectively, showing no statistically significant difference (*P* = 0.091).

Table 1 Mean TDT, TRT, fever, ESR, CRP, LC, and ANC in two groups of patients with and without abnormal DMSA scan

Factor	DMSA	Mean	SD	<i>P</i> value
TDT (h)	Normal	53.6	37.7	0.001
	Abnormal	84.6	53.3	
TRT (h)	Normal	23.5	13.7	0.001
	Abnormal	47.4	27.3	
Fever (°C)	Normal	38.5	0.7	0.001
	Abnormal	39.1	0.8	
ESR (mm)	Normal	39.7	28.6	0.003
	Abnormal	58.5	32.8	
CRP (mg l ⁻¹)	Normal	16.8	15.2	0.004
	Abnormal	32.7	27.5	
LC (mm ⁻³)	Normal	12520	3774	0.001
	Abnormal	17348	7246	
ANC (mm ⁻³)	Normal	7674	3939	0.001
	Abnormal	12384	6931	

TDT therapeutic delay time, *TRT* therapeutic response time, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *LC* leukocyte count, *ANC* absolute neutrophil count

Mean TDT, TRT, fever, ESR, CRP, LC, and ANC in the two groups of patients with and without abnormal DMSA scan findings are shown in Table 1. ROC curve analysis was performed to reach to the best cut-off values for ESR, CRP, LC, ANC and fever. The diagnostic utility of these factors is shown in Table 2.

Table 3 depicts different clinical, biological and laboratory values that were found to be predictive of abnormal ^{99m}Tc-DMSA findings using univariate analysis. Considering that some of these parameters may not have a direct effect on abnormal ^{99m}Tc-DMSA scan findings and that their effects are possibly caused by their indirect action via another parameter, a multivariate logistic regression analysis was done.

Multivariate logistic regression analysis was performed using independent variables that were shown to have a statistically significant contribution in the univariate analysis. The result of this analysis which was done on 64 cases (which had complete information for all different variables) is given in Table 4. After multivariate analysis only five variables predicted the presence of abnormal DMSA renal scintigraphy findings as independent factors.

In 11 cases abnormal ^{99m}Tc-DMSA scintigraphic findings were noted bilaterally. There was no significant difference in the clinical, biological and laboratory values comparing the two groups of patients with unilateral and bilateral renal involvement, except for ANC which showed marginal statistical significance (Table 5).

Discussion

One of the problems in the interpretation of DMSA renal scintigraphy is the inability to differentiate new renal lesions from the old scars. To overcome this limitation, all children with the history of previous UTI were excluded from the study. DMSA renal scintigraphy has been proven as the gold standard for the diagnosis of acute pyelonephritis (APN) [5, 12]. Clinical applicability of various inflammatory markers (LC, ANC, CRP, ESR) for the diagnosis of APN has been previously determined and compared with the DMSA scan findings as the gold standard [5]. The current study again shows that these inflammatory markers have limited value for the diagnosis of APN (Table 2).

Fernández-Menéndez et al. [5] reported the sensitivity of LC, ANC, CRP, and ESR to be 57, 61, 79

Table 2 Diagnostic utility of different inflammatory and clinical parameters

	Cut-off value	Sensitivity	Specificity	PPV	NPV	Area under the curve ^a
ESR (mm)	40	69.7	58.5	75.7	51.1	0.668
CRP (mg l ⁻¹)	30	52.4	77.3	81.5	45.9	0.659
LC (mm ⁻³)	13500	70.1	61.5	78.2	51.1	0.700
ANC (mm ⁻³)	9000	65.3	61.5	76.5	48.0	0.704
Fever (°C)	39	64.0	69.0	78.7	51.8	0.724

PPV positive predictive value, *NPV* negative predictive value, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *LC* leukocyte count, *ANC* absolute neutrophil count

^a Only the significant values are shown

Table 3 Predictive factors for the presence of abnormal ^{99m}Tc-DMSA findings in patients with first episode of urinary tract infection: univariate analysis

Predictive factor	n	P value	OR	95% CI	RR	95% CI
Age ≥ 18 months	119	0.001	3.90	1.75–8.71	2.43	1.41–4.19
Female gender	119	0.94	1.04	0.42–2.59	1.03	0.57–1.86
Axillary temperature ≥ 39°C	119	0.001	3.97	1.77–8.88	2.43	1.41–4.19
TDT ≥ 48 h	101	0.008	3.19	1.33–7.65	2.06	1.22–3.50
TRT ≥ 24 h	95	0.001	5.03	1.85–13.66	2.58	1.52–4.38
Species other than <i>E. coli</i>	119	0.33	1.50	0.50–4.55	1.32	0.60–2.90
LC ≥ 13500 mm ⁻³	119	0.001	3.76	1.67–8.44	2.35	1.39–3.98
ANC ≥ 9000 mm ⁻³	119	0.005	3.02	1.35–6.72	2.05	1.21–3.47
CRP ≥ 30 mg l ⁻¹	64	0.021	3.74	1.17–12.01	2.48	1.05–5.89
ESR ≥ 40 mm 1st hour	117	0.003	3.25	1.48–7.18	2.10	1.28–3.47
Ultrasonographic abnormality	105	0.001	14.47	1.84–113.56	8.28	1.22–56.35
Presence of organ-specific complaints	119	0.284	1.41	0.60–3.33	1.24	0.74–2.09
Moderate or high VUR	71	0.029	5.03	1.03–24.56	3.19	0.86–11.88

OR odds ratio, CI confidence interval, RR risk ratio

Table 4 Predictive factors for the presence of abnormal ^{99m}Tc-DMSA findings in patients with first episode of urinary tract infection: multivariate analysis

Predictive factor	OR	95% CI	RR	95% CI
Age ≥ 18 months	5.68	1.20–28.87	1.72	1.09–1.97
TDT ≥ 48 h	4.93	1.00–24.23	1.71	1.05–1.99
TRT ≥ 24 h	6.17	1.01–37.85	2.05	1.04–2.46
Axillary temperature ≥ 39°C	8.09	1.85–35.39	1.84	1.31–2.02
LC ≥ 13500 mm ⁻³	5.33	1.21–25.31	1.71	1.06–1.96

OR odds ratio, CI confidence interval, RR risk ratio

and 69%, respectively, while their specificities were 65, 61, 55, and 69%, which are very similar to those of the current study. They concluded that these inflammatory markers have limited value for the diagnosis of APN.

Most studies have reported limited sensitivity and high specificity of ultrasonography for the diagnosis of APN in the early phases of the illness [13], which was also found in our study (26.5%). However, considering its safety and its ability to diagnose concomitant renal anomalies, ultrasonography is still indicated in patients with UTI as one of the earliest diagnostic procedures.

Our study similar to the study, conducted by Martin Aguado [14], showed that children’s higher age at the time of presentation is one of the predictors of abnormal DMSA finding. This may suggest the

Table 5 Mean value of different clinical and laboratory factors in patients with unilateral versus bilateral renal involvement

Factor	Renal involvement	Mean	SD	P value
TDT (h)	Unilateral	85.7	53.8	0.685
	Bilateral	78.5	52.7	
TRT (h)	Unilateral	46.1	25.5	0.392
	Bilateral	53.9	35.8	
Fever (°C)	Unilateral	39.1	0.8	0.373
	Bilateral	39.3	0.8	
ESR (mm)	Unilateral	59.3	33.4	0.591
	Bilateral	53.6	29.6	
CRP (mg l ⁻¹)	Unilateral	33.0	27.7	0.942
	Bilateral	32.0	29.5	
LC (mm ⁻³)	Unilateral	16765	6577	0.220
	Bilateral	20851	10104	
ANC (mm ⁻³)	Unilateral	11730	6578	0.048
	Bilateral	16184	8016	

importance of more aggressive evaluation of older children presenting with UTI.

Fernández-Menéndez et al. [5] found the bacterial pathogens others than *E. coli* as a predictive factor for DMSA abnormal findings. However, we did not find such correlation which is similar to the results obtained by Goldman et al. [15].

In the current study, fever (≥39°C) was found to be a predictive of abnormal DMSA scan findings. This is similar to the findings of Fretzayas et al. [16]. They

found that the sensitivity and specificity of fever $\geq 38^{\circ}\text{C}$ as a predictor of DMSA abnormalities are 86 and 64%, respectively. Conversely, Krzemien et al. [17] and Biggi et al. [18] found no such correlation between fever and DMSA scan abnormalities.

Also, Kotoula et al. [19] reported that body temperature of 38°C , as well as a history of diarrhea and poor oral intake, is more common in patients with abnormal DMSA scan findings. They also reported the value of procalcitonin (PCT) for the diagnosis of upper versus lower UTI with reasonably high sensitivity, specificity, and positive and negative predictive values (89, 97, 96, and 91%, respectively), which were more than those of the conventionally used lab tests such as ESR and CRP. Unfortunately, we did not use PCT in our study.

Fernández-Menéndez et al. [5] reported a sensitivity and specificity of 69 and 46% for an ESR cut-off value of 30 mm 1st hour, while we found approximately similar sensitivity and specificity (69.7 and 58.5%) for an ESR cut-off value of 40 mm 1st hour. The higher ESR in our study may be justified by the presence of anemia (hemoglobin = 10.9 ± 1.5 and hematocrit 12.9 ± 4.6) in our study population (possibly caused by malnutrition) which can falsely increase the patients' measured ESR. This should be kept in mind when using ESR as a marker of an underlying inflammatory or infectious process in patients with possible anemia.

Several studies have evaluated the association between VUR and DMSA abnormalities, yielding different results. Biggi et al. [18], Fernández-Menéndez et al. [5] and Soylu et al. [20] found an association between high grade VUR and an abnormal DMSA renal scan. Although VUR is a famous predisposing factor for the development of APN, some recent studies have questioned such predisposition. Mena et al. [21] in 2006 evaluated the relationship between VUR and abnormal DMSA renal scan findings in 230 children with UTI. In this study, 27% of renal units with VUR showed abnormal DMSA renal scan while this figure was 8% in non-refluxing renal units. They concluded that although correlation between VUR and abnormal DMSA does exist, it is not complete. More or less similar results are reported by other investigators [22, 23]. Although in our study abnormal DMSA renal scan was more frequently found in refluxing renal units as compared with the non-refluxing ones, the difference was not statistically significant ($P = 0.091$).

Special attention in the current study was paid to the time factor. This was because we believed that due to social, cultural and economical reasons, medical care seeking and patient referral to an appropriate medical center happens more sluggishly in our developing country. For this reason, TDT and TRT, the two variables that were evaluated in a few of the previous studies [5, 7–9], were used. Fernández-Menéndez et al. [5] found a longer TDT in patients with abnormal DMSA scan findings when compared with the normal ones. The result of our study confirms these findings (84.6 h vs. 53.6 h, respectively, $P < 0.001$). They [5] also found TRT to be shorter in patients with normal DMSA scan, which again is consistent with the results of our study (47.4 and 23.5 h, respectively, $P < 0.001$). This signifies the importance of time factor in the development of renal abnormalities, and response to treatment.

The mean TDT and TRT in the current study were roughly two times greater than the values reported by Fernández-Menéndez [5]. This difference possibly supports our primary concern about the sluggish patient referral in our patient population, caused by different socio-sanitary and economical conditions in our country (a developing country) as compared with the more developed ones. In developing countries, more delay is noted before patients or their families seek medical attention, thus increasing the TDT. This may also explain the lower number of normal DMSA scans in our study population.

In our study, after performing multivariate analysis, the predictive factors for the presence of abnormal DMSA scan were found to be: age ≥ 18 months, TDT ≥ 48 h, TRT ≥ 24 h, fever $\geq 39^{\circ}\text{C}$ and LC $\geq 13500 \text{ mm}^{-3}$ (Table 4). As can be seen, both time factors were strong predictive factors of APN. This once again shows the important role of time factor on the final outcome of patients with UTI.

Conclusion

TDT ≥ 48 h, TRT ≥ 24 h, axillary temperature $\geq 39^{\circ}\text{C}$, LC $\geq 13500 \text{ mm}^{-3}$, and age ≥ 18 months predicted the presence of abnormal DMSA scan in patients with first episode of UTI.

Higher TDT and TRT and the higher prevalence of abnormal DMSA renal scan findings in our study as compared to the previous ones possibly signifies the

more important role of time factor in developing countries as compared with the more developed ones. Thus, due to their special socio-sanitary and economical conditions, more timely and aggressive management of children with UTI may be necessary in such countries.

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