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Which Factors Related to the Renal Cortical Defects in Infants Under 3 Months of Age with Urinary Tract Infections?

Yu Kyung An, M.D.
Myung Hyun Cho, M.D.
Kyo Sun Kim , M.D., Ph.D.

Department of Pediatrics, Konkuk University Hospital, Seoul, Korea

Corresponding author: Kyo Sun Kim, M.D, Ph.D.
Department of Pediatrics, Konkuk University Medical Center, 120-1 Neungdong-ro (Hwayang-dong), Gwangjin-gu, Seoul 05030, Korea
Tel: +82-2-2030-7551
Fax: +82-2-2030-7748
E-mail: 19890009@kuh.ac.kr

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Purpose: We used technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy to identify factors predictive of renal cortical defects in infants <3 months of age with urinary tract infections (UTIs).
Methods: We retrospectively reviewed data on infants <3 months of age with culture-proven UTIs treated at a single center from March 2010 to February 2016. Blood samples were obtained for laboratory evaluation prior to commencement of antibiotic therapy. The therapeutic delay time (TDT) and therapeutic response time (TRT) were recorded. All patients were divided into two groups depending on features of their DMSA scans. We compared the demographic, clinical, and laboratory characteristics of the two groups.
Results: A total of 119 infants (94 males and 25 females; mean age, 56.9±21.3 days) were included. Cortical defects were evident in the DMSA scans of 47 cases (39.5%). In infants with such defects, the peak temperatures (38.9±0.57℃ vs. 38.4±0.81℃, *P*=0.001), the absolute neutrophil counts (8,920±4,460/mm vs. 7,290±4,090/mm, *P*=0.043), and the C-reactive protein (CRP) levels (6.49±4.33 mg/dL vs. 3.21±2.81 mg/dL, *P*=0.001) were significantly higher than those in infants without cortical defects. The TDT was also longer in those with cortical defects (*P*=0.037).
Conclusion: We found that a TDT ≥8.5 hr (odds ratio [OR] 5.81), a peak temperature ≥38.3℃ (OR 6.19), and a CRP level ≥4.96 mg/dL (OR 7.26) predicted abnormal DMSA scan results in infants <3 months of age with UTIs.

Key words: Urinary tract infection, Pyelonephritis, Technetium Tc 99m dimercaptosuccinic acid

Introduction

Urinary tract infections (UTIs) are the most frequent severe bacterial infections in pediatric populations, especially infants[1]. One study found that 85% of serious bacterial infections in infants <90 days of age were UTIs[2]. UTIs are classified into pyelonephritis and cystitis. Such discrimination is necessary because renal parenchymal injury may induce permanent renal scarring[3], in turn causing hypertension, chronic renal failure, and end-stage renal disease [4]. Clinical and experimental studies have shown that renal scarring can be prevented or diminished by vigorous treatment of acute pyelonephritis

(APN)[5]. Presentation with fever, vomiting, lethargy, and irritability is suggestive of APN. However, these signs and symptoms are vague, nonspecific, and misleading in pediatric populations, especially neonates and young infants [6]. Technetium-99m dimercaptosuccinic acid (DMSA) scan is the most effective technique for the diagnosis of acute kidney lesions[7]. However, DMSA scan as UTI workup is becoming increasingly unpopular[8,9]. Recent UTI guidelines issued by the National Institute of Health and Clinical Excellence suggest that a selective approach be taken toward imaging; routine DMSA scanning is not recommended for infants <6 months of age when they respond well to antibiotic treatment within 48 hr[10]. Moreover, even if DMSA scanning is considered desirable, many hospitals may not have equipment suitable for evaluation of children.

Prediction of who will and will not develop clinically significant renal lesions remains challenging. It is important to identify the most effective mode of evaluation in order to not subject patients to unnecessary procedures. Infants are more prone to develop permanent renal damage than are older children because inflammatory reactions are especially harmful during the period when kidney growth is most rapid[11]. We identified factors associated with the risk of APN development in infants <3 months of age.

Materials and methods

1. Study population

We retrospectively analyzed data on infants <3 months of age who were admitted to Konkuk University Hospital between March 2010 and February 2016 with first-episode febrile UTIs. Gender, age, clinical manifestations, laboratory findings, culture results, and imaging findings were collected by review of medical records. UTI was diagnosed based on fever (axillary temperature ≥38℃) and a positive urine culture, defined as a single microorganism present at $>5\times10^4$ colony-forming units/mL in a specimen obtained via catheterization. Patients with previous histories of UTI were excluded because old and new lesions evident on DMSA scans could not be clearly distinguished. Also, patients who gave blood samples after antibiotic administration were excluded. Blood samples were usually collected before intravenous antibiotic treatment commenced.

The therapeutic delay time (TDT) was defined as the number of hours from the onset of fever to administration of the first dose of an appropriate antibiotic and the response time (TRT) was the number of hours from the first dose of antibiotic to fever remission (defined as a temperature <37.5 ℃ sustained without any need for an antipyretic).

2. Imaging

Imaging was performed on all patients with confirmed UTIs. DMSA scintigraphy was performed within the first 7 days of treatment to explore renal involvement. The extent of each renal lesion was determined by examining four different views of the lesion. They served to allow evaluation of differential renal function, kidney size, and cortical uptake, with or without bulging contours. We divided all patients into two groups depending on their DMSA findings.

All infants underwent renal ultrasonography (US). The results were deemed abnormal if any the following was evident: dilatation of the collecting system (pelvic diameter ≥4 mm), a renal size difference >10%, ureteral dilatation, an increase in echogenicity, hydronephrosis, or thickening of the bladder wall.

Voiding cystourethrography (VCUG) was not routinely performed, although 90 patients (75.6%) underwent VCUG after a negative urine culture was obtained.

3. Statistical analysis

Quantitative variables were reported as means±standard errors and qualitative variables as frequencies with percentages. Differences in demographic and laboratory characteristics between infants with and without cortical defects were compared using the Mann-Whitney U-test. To obtain diagnostic cut-off values for laboratory or clinical factors (the TDT, peak temperature, the absolute neutrophil counts [ANC], and levels of hemoglobin [Hb], albumin, and CRP) and to identify parameters predicting the development of renal lesions, we calculated areas under receiver operating characteristic (ROC) curves. Sensitivities and specificities were also estimated.

For univariate analyses, continuous and categorical variables were analyzed using the Pearson chi-squared (χ^2) test. Variables found to be significant in univariate analysis were subjected to multivariate analysis using the stepwise logistic regression method to calculate odds ratios (ORs)

with 95% confidence intervals (CIs). Each OR was adjusted for the prevalence of APN in our study population to identify optimal predictors of renal involvement. All statistical analyses were performed with the aid of SPSS software version 23.0. A *P* value <0.05 was considered to be statistically significance.

4. Ethical approval

The current study was approved by the Institutionsl Review Board (IRB) of Konkuk University Medical Center (IRB approval protocol No. KUH1090051). Informed consent was obtained by all parents of patients

Results

A total of 119 patients with febrile UTIs were enrolled and divided into two groups on the basis of their DMSA scan data. Seventy two and 45 infants (60.5% and 39.5%) had normal and significantly abnormal scintigraphic scans, respectively. Age, gender, and duration of hospitalization did not differ between the two groups (Table 1).

Those with DMSA defects had a significantly longer TDT, a higher peak temperature, a greater ANC, a higher CRP level, and lower Hb and albumin levels, than did those without DMSA defects. Neither the TRT nor the most common isolated pathogen differed significantly between the two groups.

ROC curves were constructed to determine the optimal cut-offs of factors predicting renal parenchymal involvement (Table 2). A TDT cut-off of 8.5 hr afforded the highest sensitivity (93.62%), and a CRP cut-off of 4.96 mg/dL had the highest specificity (87.50%) and the greatest AUC (0.774). Meanwhile, a peak temperature cut-off of 38.3℃ afforded high sensitivity (85.11%) but low specificity (55.56%).

Table 3 lists the predictive factors of abnormal findings on DMSA scans. Following univariate analyses, we found statistically significant differences in peak temperature, the TDT, the ANC, and the levels of CRP and albumin at the various cut-offs; these variables were then subjected to multivariate analysis. Three parameters significantly predicted APN upon multivariate analysis: peak temperature (OR, 6.19; 95% CI, 2.17-19.91), initial serum CRP level (OR,

Table 1. Baseline Characteristics of the Patients

	DMSA defect (-) (n=72)	DMSA defect (+) (n=47)	*P*-value
Age (days)	56.9±22.9	56.8±18.9	0.973
Sex (male/female)	57/15	39/8	0.607
TDT (hours)	18.7±15.9	27.9±26.8	0.037*
TRT (hours)	13.6±30.8	19.0±29.7	0.343
Peak temperature (℃)	38.4±0.80	38.9±0.57	0.001*
Hospitalization duration (days)	6.26±2.42	6.66±2.68	0.405
WBC (x10^3/μL)	15.0±6.10	16.6±7.01	0.249
Neutrophil (%)	46.4±13.0	49.5±12.2	0.280
ANC (x10^3/μL)	7.29±4.09	8.92±4.46	0.043*
Hemoglobin (g/dL)	11.5±2.33	10.7±1.64	0.030*
PLT (x10^3/μL)	397.7±111.4	442.5±141.0	0.056
CRP (mg/dL)	3.21±2.81	6.49±4.33	0.001*
Albumin (g/dL)	3.77±0.39	3.63±0.28	0.029*
Na (mmol/L)	135.9±1.83	135.2±2.02	0.065
K (mmol/L)	5.42±0.54	6.29±6.69	0.375
tCO2 (mmol/L)	19.5±3.26	19.5±2.83	0.958
Urine culture			0.080
E. coli	61	39	
non-*E. coli*	11	8	

Values: Mean ± Standard deviation.
Abbreviations: DMSA, dimercaptosuccinic acid; TDT, therapeutic delay time; TRT, therapeutic response time; WBC, white blood count; ANC, absolute neutrophil count; PLT, platelet; CRP, C-reactive protein; Na, sodium; K, potassium; tCO2, total carbon dioxide; *E. coli*, *Escherichia coli*.
*P<0.05.

Table 2. Diagnostic Usefulness of Clinical and Biological Factors

	Cut-off value	Sensitivity (%)	Specificity (%)	AUR-ROC	95% CI	*P*-value
TDT (hour)	8.5	93.62	30.56	0.625	0.531-0.712	0.015*
Peak temperature (℃)	38.3	85.11	55.56	0.714	0.624-0.793	<0.0001*
ANC (x10^3/μL)	7530	59.57	66.67	0.623	0.530-0.710	0.0218*
Hemoglobin (g/dL)	10.5	57.45	59.72	0.601	0.507-0.689	0.0569
Albumin (g/dL)	3.7	70.21	48.61	0.616	0.523-0.704	0.0294*
CRP (mg/dL)	4.96	63.83	87.50	0.774	0.068-0.846	<0.0001*

Abbreviations: AUR-ROC, The area under the receiver operating characteristics curve; CI, confidence interval.
*P<0.05.

7.26; 95% CI, 2.60-22.09), and the TDT (OR, 5.81; 95% CI, 1.4 7-30.80). The CRP level (at a cut-off of 4.96 mg/dL) was associated with the highest OR for development of a cortical defect (Table 4).

Renal US was performed on all patients; the results did not differ significantly between the groups (20.8% vs. 36.2 %, *P*=0.065, Table 5). Additionally, VCUG was performed on 90 of the 119 infants; vesicoureteral reflux (VUR) was evident in 12 patients (13.3%), of whom 3 had normal DMSA scans and 9 scans showed cortical defects. These numbers did not differ significantly (*P*=0.090, Table 3).

Table 3. Predictive Factors for the Presence of Uptake Defects in Technetium-99m Dimercaptosuccinic Acid (DMSA) Scintigraphy in Infants Under 3 Months of Age with Urinary Tract Infection: Univariate Analysis

Predictive factor	OR	95% CI	*P*-value
Male (gender)	0.779	0.29-1.98	0.607
Age (days)	1	0.98-1.02	0.973
Duration of hospitalization (days)	1.064	0.92-1.23	0.404
Peak temperature ≥38.3℃	7.143	2.96-19.36	0.001*
TDT ≥ 8.5 hours	6.453	2.06-28.58	0.004*
ANC ≥7.53 x10^3/μL	2.947	1.39-6.40	0.005*
Hemoglobin ≤10.5 g/dL	0.5	0.24-1.05	0.068
CRP ≥4.96 mg/dL	12.353	5.12-32.47	0.001*
Albumin ≤3.7 g/dL	0.448	0.20-0.96	0.043*

Abbreviation: OR, odds ratio.
*P<0.05.

Table 4. Predictive Factors for the Presence of Uptake Defects in Technetium-99m Dimercaptosuccinic Acid (DMSA) Scintigraphy in Infants Under 3 Months of Age with Urinary Tract Infection: Multivariate Analysis

Predictive factors	OR	95% CI	*P*-value
Peak temperature ≥38.3℃	6.194	2.17-19.91	0.001*
TDT ≥8.5 hours	5.812	1.47-30.80	0.02*
ANC ≥7.53 x10^3/μL	2.351	0.89-6.39	0.086
CRP ≥4.96 mg/dL	7.263	2.60-22.09	0.001*
Albumin ≤3.7 g/dL	0.625	0.21-1.82	0.387

*P<0.05.

Table 5. Renal Ultrasonography and Voiding Cystourethrography (VCUG) Findings according to the Renal Cortical Defects Detected by Technetium-99m Dimercaptosuccinic Acid (DMSA) Scans

	DMSA defect (-)	DMSA defect (+)	*P*-value
Ultrasonography			
Normal	57/72 (79.2%)	30/47 (63.8%)	
Abnormal	15/72 (20.8%)	17/47 (36.2%)	0.065
VCUG			
VUR	3/43 (72) (7.0%)	9/47 (19.1%)	0.090

Abbreviation: VUR, vesicourethral reflux.

Discussion

It is important to differentiate simple lower-tract UTI from UTI featuring parenchymal involvement. DMSA scintigraphy is the gold standard for detection of APN, with sensitivity of approximately 90%[12]. However, concerns about cost-effectiveness, radiation exposure, and inadequate facilities render it difficult to perform DMSA scanning on all UTI patients. Moreover, the current guidelines recommend US as the initial imaging modality; no further imaging is necessary if the US scan is normal[13]. Several previous studies have sought to identify factors predicting APN. However, we focused on infants <3 months of age. No consensus has emerged on how to predict APN in this age group.

Fever is known to be the best predictor of renal involvement in UTI. Fretzayas et al.[14] found that the sensitivity and specificity of a fever ≥38℃ as a predictor of cortical defects were 86% and 64%, respectively. In the Pecile study, 316 children aged 0-14 years with UTIs were subjected to DMSA scanning. Those with maximum temperatures >38.5℃ were at an increased risk of positive scan results compared with those with maximum temperatures <38.5℃[15]. We found that infants with cortical defects had higher peak temperatures than others (*P*=0.001). Furthermore, peak temperature was significantly related to an increased risk of kidney involvement; however, the specificity was low. There were a few infants with a body temperature of 38.3 ℃ or more had no parenchymal involvement.

We focused particularly on time factors. One study analysed 230 children with febrile UTI found that TDT as the predictive factor for acute scintigraphic lesion[16]. This finding is also in good agreement with the studies of Printza et al.[17]. In our study, infants with cortical defects evident on DMSA scans had a longer mean TDT than did others. Multivariable analysis showed that the risk of a cortical defect was higher when the TDT was >8.5 hr, indicating that treatment delay increases the risk of kidney damage. Others have not found a correlation between TDT and DMSA scan. Ghasemi et al.[18] identified that there was no significant correlation between the TDT and the results of the acute phase scan. It is not known exactly how long it

takes an inflamed kidney to become damaged, but the message is clear: early diagnosis and treatment are essential. It remains controversial whether a long TRT is associated with the development of renal damage during acute infection[19,20]. We found no significant difference between the TRT of the two groups.

In terms of early APN diagnosis, the clinical utilities of several inflammatory markers were previously compared with the DMSA scan features, however, many published studies included both young infants and older children[21]. Recently, procalcitonin level has been shown to be useful to identify febrile UTI with parenchymal involvement. Kotoula et al.[22] studied 57 children aged 2 months to 9 years with first-episode UTIs. The procalcitonin level was more sensitive and specific in terms of diagnosis of upper versus lower tract UTI than was the erythrocyte sedimentation rate or the CRP level. Also, the plasma neutrophil gelatinase-associated lipocalin (NGAL) concentration has been reported to serve as a useful diagnostic biomarker of renal injury in infants aged 1-12 months with acute febrile UTI[23].

This study found that in infants with cortical defect, serum albumin and hemoglobin were significantly lower than infants without cortical defect. One study assessed the risk factors for septic shock in patients with APN was proven that serum albumin level in the septic shock group were significantly lower than in the non-septic shock group. Hypoalbuminemia is thought to develop secondarily to various disease states and to be associated with increased albumin turnover[24]. Chen et al.[25] demonstrated that UTI infants had low level of hemoglobin, explaining the potential pathogenesis including the formation of some hepatotoxins from the infected gram-negative bacilli which might increase the fragility of red blood cells and the production of hemolysin.

We selected infants <3 months of age and found that the frequency of abnormal sonographic findings did not differ significantly between the two groups (P=0.065). Those who have studied associations between the VUR and DMSA abnormalities have come to different conclusions. Benador et al.[12] in a prospective work, suggested that DMSA abnormalities were not associated with the VUR or renal malformation. The risk of APN was substantially higher in patients with high-grade VUR, raising the question as to whether routine VCUG to diagnose VUR might be an optimal predictive strategy[26,27]. Lee et al.[28] suggested that VCUG was indicated only when abnormalities are apparent on either or both of renal US and DMSA scans from children with first-episode febrile UTIs. We found that although VUR was more frequently evident in those with cortical defects, the difference was not statistically significant (P=0.090). Further studies with larger patient numbers are warranted to explore the relationships between APN and renal image data from young infants.

Our study had several limitations. First, our sample size was small. Second, we did not evaluate certain inflammatory markers such as procalcitonin and NGAL levels. Also, it was difficult to accurately record fever onset times. Instead, we relied on parental memories.

In conclusion, we found that a high peak temperature, increased levels of inflammatory markers (CRP and the ANC), and low albumin and Hb concentrations, were associated with APN in infants <3 months of age. Peak temperature afforded high sensitivity, and elevated CRP level afforded both high specificity and a greater AUC. Furthermore, delayed treatment increases the risk of such involvement. The OR for APN reached 6.194 when treatment was delayed for >8.5 hr. Neither renal US nor VCUG exhibited any significant between-group differences in terms of renal parenchymal involvement.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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