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Clinical Efficacy of a Top-down Approach for Children with a First Febrile Urinary Tract Infection

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Purpose: The aim of this study was to determine the clinical characteristics, frequency of renal abnormalities and benefits of a top-down approach in children with their first febrile urinary tract infection (UTI).

Methods: We reviewed 308 patients retrospectively who were admitted to Yeungnam University Hospital and were treated for their first febrile UTI from February 2006 to December 2013. We performed a comparative analysis of laboratory findings and results of imaging techniques including a Tc-99m dimercaptosuccinic acid (DMSA) renal scan.

Results: Among the patients, 69% (213/308) were males, and 90% (277/308) had their first UTI episode during infancy. A DMSA renal scan was performed on all patients, and showed positive findings in 60% (184/308) of cases. Laboratory indices of inflammation were significantly higher in the DMSA-positive group ($P<0.05$). There was a statistically significant difference in the age distribution between the two groups. In the DMSA-positive group, 165 patients underwent voiding cystourethrography (VCUG), and 58 (35%) cases demonstrated vesicoureteral reflux. In total, 110 patients in the DMSA-positive group, underwent repeat scanning at 6 months; 33 children (30%) demonstrated static scarring, but 77 (70%) had improved completely. The concordance of the ultrasonography (US) and VCUG was low. Older patients had more renal scarring.

Conclusion: DMSA is a sensitive method for assessing the severity of inflammation and kidney injury. However, the ability of US to predict renal parenchymal damage was limited. A top-down approach in children with their first febrile UTI showed significant value.

Key words: Urinary tract infection, Tc-99m DMSA, ultrasonography, vesicoureteral reflux

Introductions

Acute pyelonephritis (APN) is a common serious bacterial infection in childhood[1]. The main significance of APN is its association with renal scarring, which leads to acute renal parenchymal damage and subsequent permanent damage. Extensive scarring may progress to further renal injury with subsequent hypertension, decreased renal function, proteinuria, or end-stage renal disease[2]. Hypertension occurs in 10% to 20% of children with renal scarring due to APN[3]. To identify children who may be prone to renal scarring so that it can be prevented with appropriate intervention, imaging investigations

have been routinely performed following urinary tract infection (UTI).

In the early 1970s, the evolving concept of reflux nephropathy linked the vesicoureteral reflux (VUR) to pyelonephritis and late renal scarring[2]. Children who had febrile UTI were routinely evaluated for urinary tract abnormalities including VUR with ultrasonography (US) and voiding cystourethrography (VCUG) and often received long-term antibiotic prophylaxis, and surgical correction of VUR became standard care.

US is appealing as a method of evaluation following UTI, but its ability to detect upper urinary tract abnormalities is limited. Although US is noninvasive and sufficiently sensitive to evaluate collecting system dilatation, it is less sensitive than VCUG and Tc-99m dimercaptosuccinic acid (DMSA) renal scanning in detecting VUR and parenchymal lesions[4]. VCUG is the gold standard for detecting VUR. However, it requires catheterization of the urethra and serial imaging during filling and voiding to detect the VUR[1].

These limitations combined with the increased clinical experience with DMSA renal scans has led some to advocate a novel paradigm when evaluating children with a UTI, termed the "top-down approach", which focuses on identifying children at risk for renal scarring, whether or not VUR is present, compared with the recommended scheme that proposes identifying all VUR. On the other hand, the classic "bottom-up approach" which performed VCUG initially.

A DMSA renal scan is highly sensitive for identifying renal parenchymal defects, and studies that have investigated the etiology of renal scarring provide convincing clinical evidence that renal parenchymal infection is a prerequisite for renal scarring. Recent studies of children with low-grade VUR showed no differences in risk for a UTI between antibiotic prophylaxis and no treatment[5,6], and support the "top-down approach".

The aim of this study was to describe the clinical characteristics and the role of DMSA in the detection of late damage by comparing scintigraphic findings with conventional clinical/laboratory parameters, US, and VCUG as commonly conducted diagnostic tests to localize the site of the first febrile UTI in children.

Materials and methods

We retrospectively reviewed 308 patients (213 boys and 95 girls) who were admitted to Yeungnam University Hospital and were treated for their first febrile UTI from February 2006 to December 2013.

Clinical characteristics, laboratory findings, such as white blood cells (WBC), hemoglobin, platelets, aspartate aminotransferase, alanine aminotransferase, erythrocyte sedimentation rate, C-reactive protein (CRP), radiological data, and antimicrobial susceptibility of all children were analyzed. Acute febrile UTI was clinically diagnosed as fever, urinalysis showing pyuria, or a positive urine culture, which was obtained by suprapubic aspiration or bladder catheterization.

Patients with UTI underwent DMSA renal scans and US on admission, with VCUG performed soon after the fever had subsided and infection had been controlled. APN was confirmed as an acute abnormal renal cortical defect on DMSA renal scanning. According to the presence of abnormalities detected with DMSA, we divided the subjects into DMSA-positive and DMSA-negative groups. Then, we compared clinical parameters and associated renal abnormalities between the groups.

DMSA renal scanning was performed at admission and 6 months after treatment of APN. An acute photon defect was defined as decreased isotope uptake, and renal scarring was defined as persistent changes at the same location as on the first DMSA renal scan. We analyzed patients according to the presence of renal scars in the follow-up DMSA renal scan.

Doppler US scans were interpreted without previous knowledge of the DMSA renal scan findings. US could identify the presence of anatomical abnormalities, hydronephrosis, pelvic dilatation of the ureter, and increased or decreased cortical echogenicity. Reduced renal blood flow on Doppler US was considered to indicate ischemic injury.

VCUG was performed after confirmation of negative follow-up urine culture, 1-2 weeks after infection had been controlled. VUR was classified according to the international VUR classification. If tracking was possible during the study period, for the patients who has abnormal findings with DMSA or US and who had repeated UTI, the VCUG was repeated a year later.

Statistical analysis was performed using the SPSS software (ver. 21.0). Data were compared using Student's t-test, Fisher's exact test, linear-by-linear association, and kappa coefficient values. *P*-values <0.05 were considered to indicate statistical significance.

Results

1. Patient characteristics

In total, 308 children (213 boys and 95 girls; age, 1-108 months; mean, 7.9±15.3 months) with their first episode of a UTI were included in the study. Among these patients, 49% (151/308) were aged <3 months and 90% (277/308) were <12 months at the time of the UTI diagnosis (Table 1).

According to abnormalities on the initial DMSA renal scan, the study subjects were divided into the DMSA-positive group (n=184) and the DMSA-negative group (n=124).

2. Laboratory findings

WBC count was significantly different between the groups (16,490±6,347 vs. 13,347±4,955/mm^3, *P*<0.001). The DMSA-positive group had a higher CRP level than the DMSA-negative group (6.0±5.2 vs. 2.8±2.6 mg/dL, *P*<0.001). No difference was found in ESR between the groups (Table 1).

Cultures were obtained by suprapubic aspiration or urethral catheterization. The predominant urinary tract pathogen was *E. coli* (89%), followed by *Enterococcus* (4%), and *Klebsiella pneumoniae* (4%). *Enterobacter cloacae, Streptococcus agalactiae*, and *Pseudomonas* were also found.

Table 1. Demographics and Laboratory Data of the Patients

Data	DMSA positive (n=184)	DMSA negative (n=124)	*P*-value
Gender			
Male:Female	122:62	91:33	0.187
Age (Mo)	10.0±18.2	4.9±8.8	0.001
Age distribution			
0-3 months	75 (41%)	76 (61%)	<0.001
4-12 months	82 (45%)	44 (36%)	
13-24 months	10 (5%)	0 (0%)	
>24 months	17 (9%)	4 (3%)	
WBC (/μL)	16,490±6,347	13,347±4,955	<0.001
CRP (mg/dL)	6.0±5.2	2.8±2.6	<0.001
ESR (mm/H)	66.8±166.0	38.4±133.6	0.135

Abbreviations: DMSA, Tc-99m dimercaptosuccinic acid; WBC, white blood cell count; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate.

3. *Kappa* coefficient for DMSA renal scans and Doppler ultrasonography

Doppler US showed abnormal findings in 97/184 (52.7%) in the DMSA-positive group, whereas 100/124 (80.6%) in the DMSA-negative group had normal findings (Table 2). The *kappa* coefficient, which is used to test interrater reliability, for DMSA renal scans and Doppler US was low (κ= 0.308).

4. Voiding cystourethrography

VCUG was performed in 202 patients. One hundred sixty-five patients in the DMSA-positive group (n=184) and 37 patients in the DMSA-negative group (n=124) checked VCUG. About 35% (58/165) of patients in the DMSA-positive group had VUR, whereas only 13% had VUR in the DMSA-negative group (*P*=0.02). Of the patients with VUR, 79% (46/58 in the DMSA-positive group and 4/5 in the DMSA-negative group) had grade 3 or higher VUR (Table 3).

Table 2. Comparison of Imaging Methods between DMSA Renal Scan and Doppler US

	DMSA positive (%)	DMSA negative (%)	Total
Doppler US			
Abnormal finding	97 (52.7%)	24 (19.4%)	121 (39.2%)
Normal finding	87 (47.3%)	100 (80.6%)	187 (60.7%)
Total	184	124	308

κ =0.308.
Abbreviations: DMSA, Tc-99m dimercaptosuccinic acid; US, ultrasonography; κ, Kappa coefficient value.

Table 3. Result of VCUG between DMSA Positive and Negative Group

	DMSA positive (n=165)	DMSA negative (n=37)	*P*-value
VUR	58 (35.2%)	5 (13.5%)	0.020
grade I	3 (5.2%)	1 (20%)	
grade II	9 (15.5%)	0 (0%)	
grade III	21 (36.2%)	1 (20%)	
grade IV	21 (36.2%)	2 (40%)	
grade V	4 (6.9%)	1 (20%)	
No reflux	107 (64.8%)	32 (86.5%)	
Total	165	37	

Abbreviations: VCUG, voiding cystourethrography; DMSA, Tc-99m dimercaptosuccinic acid; VUR, vesicoureteral reflux.

5. Doppler ultrasonography and voiding cystourethrography coefficient

No difference in the Doppler US results was detected between those who had VUR or not. Only 59% (37/63) of patients who had VUR had US abnormalities (Table 4). Moreover, 49% (68/139) of the patients without VUR showed US abnormalities. The sensitivity of US was 0.591, and the positive predictive value (PPV) was low (PPV=0.371) in the 37 children who had abnormalities on both imaging techniques. The sensitivity of VCUG was 0.352,and the specificity was 0.732.

6. Follow-up DMSA renal scan

A total of 110 children in the DMSA-positive group underwent a follow-up DMSA renal scan. Of these, 70% (77/110) showed complete improvement and 30% had some renal scarring. The mean age of the completely improved group was lower than that of the persistently abnormal group (7.2 vs. 22.1 months, *P*=0.006). When comparing children who got a follow-up DMSA by age, the complete improvement was more common in younger children (Table 5).

A follow-up DMSA was performed in the 102 patients who underwent VCUG. In follow-up DMSA renal scan, the frequency of VUR was less in the group with completely improved findings (29/70) and higher in the persistently abnormal group (19/32) (*P*=0.045). However, these results did not indicate the severity of the VUR (Table 6).

Table 4. Result of Doppler US and VCUG

		Doppler US		*P*-value
		Normal (n=97)	Abnormal (n=105)	
No VUR	139	71 (73.2%)	68 (64.8%)	
VUR	63	26 (26.8%)	37 (35.2%)	0.061
grade I	4	3 (11.5%)	1 (2.7%)	
grade II	9	5 (19.2%)	4 (10.8%)	
grade III	22	8 (30.8%)	14 (37.8%)	
grade IV	23	10 (38.5%)	13 (35.1%)	
grade V	5	0 (0%)	5 (13.5%)	

Abbreviations: US, ultrasonography; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux.

Table 5. Age Distribution of the Pateints between Persistently Abnormal Group and Completely Improved Group on Follow-up DMSA Renal Scan

	Completely improved (n=77)	Persistently abnormal (n=33)	*P*-value
Age (month)			
0-3	32 (41%)	9 (27%)	<0.001
4-12	39 (51%)	11 (34%)	
13-24	2 (3%)	3 (9%)	
>24	4 (5%)	10 (30%)	
mean age (month)	7.2	22.1	0.006

Abbreviation: DMSA, Tc-99m dimercaptosuccinic acid.

Discussion

Pyelonephritis is a common clinical problem in infants and children. It has been suggested that the inflammatory process causes irreversible renal parenchymal scarring[4], and permanent renal scarring has been observed in 15-60% of children after a UTI[2]. Community studies suggest that boys <1 year of age and girls <5 years of age are most at risk for a UTI[7]. Renal scarring found in association with VUR is an important cause of hypertension and end-stage renal disease in children[8]. Rapid antibacterial treatment can arrest or prevent the development of scarring when reflux and infection are present[8]. Paintsil proposed that the key to preventing UTI complications in children is early diagnosis and initiating the appropriate antibiotic treatment[9]. Use of antimicrobial prophylaxis is recommended based on known risks for recurrent UTI and for renal scarring should UTI occur, regardless of the presence or absence of reflux[6].

Risk factors for renal scarring in children after a UTI include age at presentation, sex, recurrent infection, peak

Table 6. Relationship of Severity of VUR between Persistently Abnormal Group and Completely Improved Group on Follow-up DMSA Renal Scan

		DMSA f/u		*P*-value
		Completely improved (n=70)	Persistently abnormal (n=32)	
No VUR	54	41 (58.6%)	13 (40.6%)	0.045
VUR	48	29 (41.4%)	19 (59.4%)	
grade I	3	1 (3.4%)	2 (10.5%)	0.434
grade II	8	2 (6.9%)	6 (31.6%)	
grade III	17	12 (41.4%)	5 (26.3%)	
grade IV	18	13 (44.8%)	5 (26.3%)	
grade V	2	1 (3.4)	1 (5.3%)	

Abbreviations: VUR, vesicoureteral reflux; DMSA, Tc-99m dimercaptosuccinic acid.

fever, treatment delay, presence of VUR, laboratory indices of inflammation, bacterial virulence, host defense factors, and genetic susceptibility[2]. Fever is the most common symptom of a UTI in infants. Moreover, the presence of another source of fever on examination, such as otitis media or other viral symptoms, does not exclude a UTI[7]. Jaksic et al. demonstrated that classical clinical and laboratory findings do not necessarily confirm a diagnosis of APN and were unable to predict the extension of kidney involvement, mainly due to the low specificity of WBC and CRP values[10]. However, in this study, the levels of WBC and CRP were significantly higher in the DMSA-positive group.

DMSA renal scanning is the most sensitive radiological approach to detect APN[11]. Jaksic et al. showed that the majority of children with a febrile UTI have abnormalities on a DMSA scan and revealed a high frequency of acute inflammatory changes on DMSA renal scans in 79% of children[10].

Jakobsson and Svensson reported that over than 90% of patients diagnosed with febrile APN and abnormalities on a DMSA recovered 5 months later[12]. Thus, persistent abnormalities on a follow-up DMSA renal scan indicate renal scar formation, and 36% of all children still had changes their DMSAs after 2 years[12]. Hansson et al. retrospectively reviewed 303 children <2 years of age who presented with their first UTI; VUR was found in 26% of the children, and 66% had abnormal DMSA scans[13]. In the present study, 60% (184/308) of the patients had abnormalities on their DMSA renal scans, which is similar to another study[14] and 31% (63/202) of the patients had VUR. VUR predisposes children with UTI to APN, and both are associated with renal scarring[2].

Paolo reported that patients ≥5 years who had a UTI had a higher incidence of APN. Moreover, the incidence of renal scars was higher in the older patients[15]. In this study, 35% (58/165) of patients had VUR in the DMSA-positive group, and 37 of 63 patients with VUR showed abnormalities on US. The sensitivity of VCUG was 0.591, and PPV was only 0.371. The presence of VUR was the only independent risk factor for renal scar formation after APN in infants. The prevalence of renal scarring is significantly correlated with reflux grade[16]. In this study, VCUG was performed in 202 patients. Significantly more patients in the DMSA-positive group had VUR. Of these, 35% (58/165) in the DMSA-positive group had VUR, but only 13% in the DMSA-negative group had one. Camacho et al. reported that 9.8% of patients with APN showed persistent renal scarring on a 6-month follow-up DMSA scan[17]. In the present study, 110 children underwent follow-up DMSA renal scans and 30% (33/100) had renal scarring. The mean age of the completely resolved group was lower than that of the persistently abnormal group (7.2 vs. 22.1 months; P=0.006).

US is non-invasive and can reveal various anatomical abnormalities, but only indirectly detects VUR. This imaging technique does not reliably detect low-grade reflux, pyelonephritis, or scarring[1]. As many as 60% of refluxes and 50% of renal scan abnormalities noted on a DMSA scan are routinely missed by US[6]. Montini et al. showed that prospective US after an initial febrile UTI failed to achieve the reliable detection of changes associated with reflux or subsequent renal damage[18]. Lee et al. reported that US performed with DMSA renal scanning has high specificity and high PPV[19]. In our study, normal US did not rule out renal parenchymal involvement; although 187 children were thought to be normal on US, 87 (47%) had abnormalities on the DMSA renal scan.

VCUG remains the gold standard for detecting VUR; however, it is invasive and requires catheterization[6]. Other concerns about VCUG include the radiation burden, associated pain and distress, and cost[1]. Tsai et al. recently assessed imaging approaches and found that the sensitivities for high-grade VUR on US alone and DMSA alone were 76.9% and 82.1%, respectively[20]. Late DMSA should be performed to evaluate the presence of permanent scars. And DMSA may be considered valuable for the follow-up of patients who had VUR, in order to check new renal scarring after recurrent UTI[21]. In our study, 102 patients who underwent VCUG received a follow-up DMSA scan. In follow-up DMSA renal scan, the frequency of VUR was less in the group with completely improved findings (29/70) and higher in the persistently abnormal group (19/32).

A DMSA scan performed during the acute phase of a UTI, followed by VCUG if the scintigraphic examination suggests pyelonephritis, is referred to as the top-down approach and focuses on putative pyelonephritis and scarring. This approach may decrease the number of VCUGs performed[1]. The top-down approach focuses on kidney invol-

vement during a UTI with the goal of confirming or ruling out APN. Proponents of the top-down approach recommend the use of renal US and a renal DMSA scan first[9]. Use of a targeted imaging approach for evaluating a febrile UTI in children may lead to improved resource use and reduced potentially harmful procedures and interventions without affecting the outcome of UTI in children[9]. A DMSA renal scan is the most reliable tool for the establishment of the diagnosis of APN during febrile UTI acute phase[21].

This study was performed on a small group of children and was retrospective. In our patients, VCUG was not carried out in the DMSA-negative group and we could not evaluate the incidence of VUR precisely in the group. In conclusion, an initial DMSA renal scan is a sensitive method for imaging diagnosing APN in children. Clinical, biological, and US parameters do not identify renal scarring in children. Children with a negative DMSA renal scan require no further evaluation unless a recurrent febrile UTI occurs, in which case VCUG should be performed. We reconfirmed DMSA renal scanning as an imaging technique of choice for estimating the presence of acute parenchymal changes.

Conflicts of interest

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

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