British Journal of Medicine & Medical Research
4(9): 1864-1872, 2014

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Risk Factors for Vesicoureteral Reflux in Children with Upper and Lower Urinary Tract Infections

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Authors' contributions

This work was carried out in collaboration between all authors. Author IKB designed the study, wrote the protocol and wrote the first draft of the manuscript. Author ND managed the analyses of the study, managed the literature searches. Author MOB wrote the protocol. Author BS designed the study. Author SR collected the data of patients. Author GK drawn the graphs. Author ZHG edited the grammar and language. Author SM designed the study. All authors read and approved the final manuscript.

Original Research Article

Received 30th October 2013
Accepted 30th December 2013
Published 9th January 2014

ABSTRACT

Objective: Urinary tract infections (UTIs) are common in children and may signal vesicoureteral reflux (VUR). This study aimed to identify the risk factors associated with VUR and to emphasize value of diagnostic imaging studies in children.
Methods: This study was assessed 173 medical records of children who had first-time UTI in Ege University Pediatric Nephrology Department between January 2008 and January 2010. Patients were divided into 2 groups according to localization of UTI infections. Patients with fever, elevated acute phase reactants, low urine osmolarity and positive urinary culture were defined as having an upper UTI (Group I). Patients without systemic symptoms were defined as having a lower UTI (Group II).
Results: Ultrasonography (US) findings were abnormal in 43.4% patients. Abnormal dimercaptosuccinic acid (DMSA) was detected in 45% of patients and VUR was found in 41%. US had 52.4% sensitivity and 64.4% specificity for cortical defects in DMSA, and

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52.4% sensitivity and 46.4% specificity for VUR. In Group I, DMSA had 70% sensitivity and 70% specificity for reflux in voiding cystourethrography. In Group II, US had 53% sensitivity and 48% specificity for cortical defects in DMSA, and 50% sensitivity and 41% specificity for VUR. DMSA had 62.5% sensitivity and 54.5% specificity for VUR.
Conclusions: Patients with UTIs should not be evaluated according to age and localization, only but rather according to all risk factors.

Keywords: Urinary tract infection; vesicoureteral reflux; diagnostic tools; renal scar; children.

1. NTRODUCTION

Urinary tract infections (UTIs) are common in children. UTIs are diagnosed by the isolation of pure bacterial growth in an uncontaminated sample of urine [1,2]. The cumulative prevalence of UTIs in the first 8 years of life is 2% in boys and 8% in girls [2,3]. UTIs may result in serious complications both early and long-term, such as renal scarring, hypertension, renal failure, and complications in pregnancy [1,2,4,5]. UTIs may signal underlying urological abnormalities, especially vesicoureteral reflux (VUR) [1,2,4]. Renal scarring occurs in almost 30% of these cases [6]. Hypertension develops in 10–30% of children and young adults with renal scarring (1). VUR is associated with 7–17% of children diagnosed with end-stage renal disease (ESRD) worldwide [7]. Reflux nephropathy accounts for 25% of children with ESRD requiring chronic dialysis or renal transplantation [6].

Early diagnosis is very important for reducing and preventing complications [8]. However, current recommendations for imaging patients with UTIs are problematic [1,8,9].

Therefore, the identification of risk factors for VUR is very important. There are different imaging modalities in primary UTI. The objective of this study was to identify the risk factors associated with VUR and to identify the value of diagnostic imaging studies in children with UTIs.

2. MATERIALS AND METHODS

A total of 173 children with a first-time UTI were enrolled in this retrospective study during 2-year period at Ege University Pediatric Nephrology Department.Patients were divided into 2 groups according to age (≤6 months and >6 months). Patients with fever, elevated acute phase reactants (including white blood cells [WBC], C-reactive protein [CRP]), low urine osmolarity, pyuria and positive urinary culture were accepted as having an upper UTI (n=133, 77%; Group 1). Patients without systemic symptoms were evaluated as having a lower UTI (n = 40, 33%; Group 2).

We performed both a dimercaptosuccinic acid (DMSA) test and ultrasonography (US) in patients with upper UTI. We also applied voiding cystourethrography (VCUG) in the patients who had scarring and abnormal US findings.

Patients were excluded if they had a history of previous UTI, renal or bladder disease, immunodeficiency concurrent extra renal infection, renal transplantation and those with chronic diseases, such as neurological abnormalities, metabolic diseases, chromosomal abnormalities, and congenital heart diseases.

Radiological investigations were performed according to treatment response and UTI type. Demographical, clinical, laboratory, and radiological data were recorded (US/VCUG/DMSA). Laboratory tests routinely performed for the identification of infection in all cases included peripheral WBC, urea, creatinine, CRP, urinalysis, and urine culture.Urine samples were taken with urine bag, placed with a fresh one every 30 minutes until urine was passed in children without urination control. Samples from children having urine control were taken from midstream voiding. Taken samples were cultured without wasting time. CRP was measured by nephelometry. Urinalysis was performed using dipstick analysis, which included a dipstick for leucocyte esterase and nitrite and/or microscopy for leucocytes and bacteria. Urine leucocytes were microscopically counted in centrifuged urine. Leukocyturia was defined as ≥5 WBC per high-power field. The diagnosis of UTI was confirmed by the presence of significant bacterial culture of a properly collected urine sample. Clinical findings and addition to a single type multiplication of bacteria more than 100.000 colonies/ml in cultures were based for diagnosis of urinary tract infections [10,11].

Renal US was performed on all patients to detect anomalies of the urinary tract. Bilateral renal length and pelvicaliceal or ureteric dilatation was assessed on US.

DMSA scans were performed with high-resolution planar imaging. Anterior, posterior, right, and left oblique images were evaluated. Normal radioactive marker uptake in the kidneys was defined as a normal scan. The presence of impaired uptake defects (focal or multifocal) on the renal parenchyma was defined as abnormal DMSA. Renal scar was defined as presence of one or more areas of focal renal cortical defects associated with defects in the renal outline, little or no DMSA uptake and loss of volume in the previous involved cortex. Any hypoactive area with preserved renal outline was defined as inflammation.

VUR was graded according to the International Reflux Study Committee Grading System as grade I to V; grades I and, II VUR were classified as low- grade reflux, while grades III, IV, and V VUR were classified as high-grade reflux.

The University Ethical Research Committee approved the study. The Statistical Package for Social Sciences (SPSS), version 15.0 for Windows, was used for the statistical analyses. Multivariate analysis and logistic regression analysis were done. Statistical significance was set at $p < 0.05$. Confidence intervals (CI) were calculated as a 95%.

3. RESULTS

We included 173 patients (120 girls and 53 boys) with first-time UTI in this study. The patients' ages ranged from 2 months to 16 years. A total of 53 patients were ≤6 months, and 120 patients were >6 months old. Of the study population, 133 (76.8%) patients had upper UTI, and 40 (23.2%) patients had lower UTI.

Leucocyte esterase was positive in 133 (76.9%) patients, while nitrite testing was positive in 95 (54.9%) patients.

All patients underwent renal US. US were normal in 98 (56.6%) patients and abnormal in 75 (43.4%) patients. A dilated renal pelvicaliceal system was found in 52 (30%) patients. Other US abnormalities were found in 23 patients, including duplex kidney (10 patients), unilateral small kidney (3 patients), unilateral renal agenesis (3 patients), renal ectopic (2 patients), ureteral dilatation (2 patients), nephrolithiasis (1 patient), increased renal echogenicity (1patient) and unilateral kidney cyst (1 patient). Abnormal DMSA findings were detected in

78 (45%) patients. VCUG was performed in 130 patients. VUR was found in 71 (41%) patients (Fig. 1). Among the patients with a dilated renal pelvis, VUR was found in 24 (grade V in 2, grade IV in 4, grade III in 5, grade II in 6, and grade I in 6 patients).

In Group I, the mean age at disease onset was 3.7 years (min–max: 2 months to 16 years). Ninety-two (69.2%) patients were boys, and 41 (30.8%) were girls. Forty-three patients (32.3%) were ≤6 months old, while 90 (60.9%) patients were >6 months old.

Abnormal renal US findings occurred in 54 (40.6%) patients, while 79 (59.4%) patients had normal US findings. Cortical defects in DMSA were detected in 61 (45.9%) patients (Fig. 1).

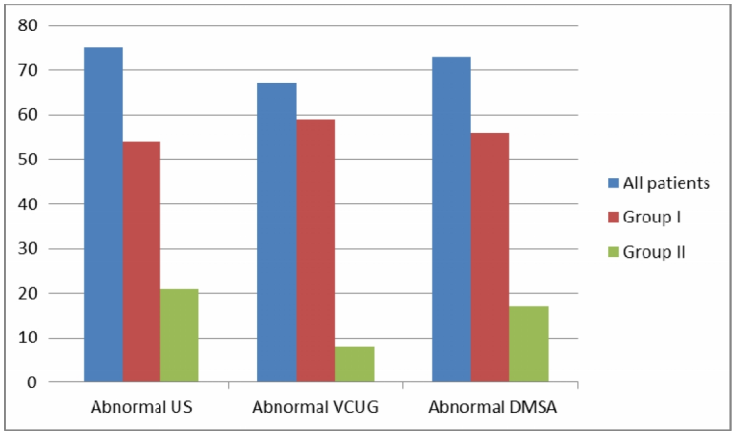

Fig. 1. Radiological findings

US, ultrasonography; VCUG, voiding cystourethrography; DMSA, dimercaptosuccinic acid

In patients with normal renal US, DMSA revealed cortical defects in 29 (37%) patients. US had 52.4% sensitivity and 64.4% specificity for cortical defects in DMSA and 52.4% sensitivity and 46.4% specificity for VUR (Table 1).

Table 1. Sensitivity and Specificity of US for abnormal ^{99m}Tc-DMSA and abnormal VCUG

	Abnormal ^{99m}Tc-DMSA (95% CI),%	Abnormal VCUG (95% CI),%
Group I		
US sensitivity	52.4	52.4
US specificity	64.4	46.4
Group II		
US sensitivity	53	50
US specificity	48	41

US: Ultrasonography, ^{99m}Tc-DMSA Dimercaptosuccinicacid, VCUG: Voiding Cystourethrography

According to our criteria, 5 variables were included in multivariate analysis: fever, elevated CRP, decreased osmolarity, fever + elevated CRP, and fever + elevated CRP + decreased osmolarity. After adjustment by multivariate analysis, fever and elevated CRP (Odds ratio [OR], 1.57; 95% CI, 1–2.3; P = 0.01) remained associated with renal scarring (Table 2).

Table 2. Risk factors for abnormal dimercaptosuccinic acid (^{99m}Tc-DMSA)

	Abnormal ^{99m}Tc-DMSA %	Normal ^{99m}Tc-DMSA %	P	OR (CI %)
Fever				
All age groups	24.8	17.3	0.013	1.62
<6 months	30.2	11.6	0.1	1.5 (0.94–2.7)
>6 months	22.2	21.1	0.15	1.6 (0.9–2.7)
Fever+ positive laboratory				
All age groups	38.3	14.3	0.00	4.5
<6 months	55.8	16.3	0.00	9.2 (1.6- 62.1)
>6 months	30	13.3	0.00	5.5 (5.3- 22.3)

Positive laboratory: Elevated C - reactive protein, White Blood Cell and decreased osmolality

VCUG was performed in 116 patients. VUR was found in 63 children (47.3%). Twenty-seven (43%) patients had VUR with a worst side of grade III or above. In patients with normal DMSA, VCUG revealed reflux in 19 (32%) patients. DMSA had 70% sensitivity and 70% specificity for reflux in VCUG. The presence of a cortical defect was a risk factor for VUR (OR, 5.3; 95% CI, 2.4–11; P = 0.00) (Table 3).

Table 3. Sensitivity and specificity of DMSA for the detection of vesicoureteral reflux

	Abnormal VCUG (95% CI), %
oup I	
^{99m}Tc-DMSA sensitivity	70
^{99m}Tc-DMSA specificity	70
Group II	
^{99m}Tc-DMSA sensitivity	62.5
^{99m} Tc-DMSA specificity	54.5

^{99m}Tc-DMSA Dimercaptosuccinicacid, VCUG: Voiding Cystourethrography

In Group II, the series consisted of 28 girls and 12 boys with a mean age of 3.5 years at admission (10 patients were ≤ 6 months of age, 30 patients were >6 months of age). Twenty-one patients had abnormal US findings. Renal scarring was detected in 17 (42.5%) patients. VUR was found in 8 (20%) patients (Fig. 1).

In patients with normal renal US, DMSA revealed cortical defects in 42% patients and VUR was detected in 30% patients. US had 53% sensitivity and 48% specificity for cortical defects in DMSA and 50% sensitivity and 41% specificity for VUR (Table 1). In addition, 33% of children with renal scarring and 20% of those without renal scarring had VUR (2 patients had grade II, 1 patient had grade III). DMSA had 62.5% sensitivity and 54.5% specificity for VUR (Table 3).

4. DISCUSSION

The correct and proper protocol for UTI in the childhood period remains unknown and is still under discussion. This study is important as it was designed to determine the required performance of imaging techniques in patients with first-time UTI. Children with UTI may have VUR (5). The aim of this study was to identify the risk factors associated with VUR and to identify the value of diagnostic imaging studies in children with UTI.

VUR is associated with 7–17% of children diagnosed with ESRD worldwide (7). Mohkam et al. [12] showed that VCUG detected VUR in 25.9% of pyelonephritis patients. Lee et al.[8] determined that VUR was detected in 30.4% (67) of patients with a first febrile UTI. Wong et al. [2] showed that VUR was detected in 23.8% of children after a first febrile urinary tract infection. Another study found VUR in 35% of children after the first UTI [13]. Our study found VUR in 41% of patients with UTI (36.4% in upper UTI and 4.6% in lower UTI). This finding is consistent with the literature. We also found that the prevalence of VUR is higher in patients with upper UTI than that of patients with lower UTI, a finding that is consistent with previous findings.

Renal US is a non-invasive first step for revealing anatomic abnormalities in patients with UTIs. Different rates (23%, 37%) have been reported in several studies of US abnormalities in children with UTIs [14]. The US findings were abnormal in 43.4% of the patients (upper UTIs, 31.2%; lower UTI, 12.2%) in our study. This result was higher than other reported values. Hydronephrosis is the most often detected urogenital anomaly [15]. Sastre et al. [15] found hydronephrosis in 34.3% of neonates with UTIs. In the present study, hydronephrosis was observed in 30% of cases. This finding was consistent with those of other studies. The prevalence of VUR was 16.2% in screened populations with prenatal hydronephrosis [16]. Other studies reported that different proportions of VUR in hydronephrosis (16.6–39%) [17]. VUR was detected in 46.1% of patients with pelvicaliceal dilatation in our study. This result was higher than the rates reported in some studies. This high rate may suggest that hydronephrosis and UTI are linked. Asl et al. reported the causes of hydronephrosis as, ureteropelvic junction obstruction (UPJO), VUR, ureterovesical junction obstruction (UVJO) and posteriorurethral valves (PUV) with the frequency of 44.5, 22.2, 8.9 and 8.9%, respectively [18]. Therefore hydronephrosis without VUR is 3 folds higher than hydronephrosis with VUR. On the other hand, in infants with UPJO, the risk of UTI is unknown, and there is a lack of prospective studies. Islek et al. [19] showed that children with UPJO, regardless of the severity of hydronephrosis had the minimal risk of UTI. In the present study, we had more than half of patients with hydronephrosis without VUR, but they all had UTI. This can be explained by other causes of hydronephrosis, primarily by PUV and bladder dysfunctions in association with.

Specificity and sensitivity of US for abnormal DMSA was different ranges [20]. Christian et al [21] reported a 22% sensitivity of renal US for the detection of renal scarring. Another study showed that US had 47.2% sensitivity for diffuse scarring and 5.2% sensitivity for focal scarring [22]. Lee et al.[8] reported 70.1% sensitivity and 71.2% specificity of US for VUR. In their study, DMSA had 70.1% sensitivity and 76.5% specificity for VUR [8]. US had 52.4% sensitivity and 46.4% specificity for VUR in our study. Further, in this study, US had 52.4% sensitivity and 64.4% specificity for cortical defects in DMSA. These results were similar to those of some studies.

DMSA scans demonstrate renal focal abnormalities and determine differential renal function [1,8,9,16]. Renal scarring occurs in 10–64% of all children with febrile UTI [1]. Hoberman [23] reported scar formation in 9.5% of pediatric patients with pyelonephritis. Lin et al. [24] published a very high scar formation rate (57%). In this study, abnormal DMSA was detected in 45.1% of patients (upper UTI, 35.2%; lower UTI, 9.8%). This result was similar to those reported in the literature.

Tseng et al. [25] determined 88% sensitivity and 36% specificity for abnormalities on DMSA scans for predicting VUR. Mohkam et al.[12] reported that DMSA had 84.1% specificity for

predicting VUR. We found that DMSA had 70% sensitivity and 70% specificity for predicting VUR on VCUG. This means that presence of a cortical defect was a risk factor for VUR (OR, 5.3; 95% CI, 2.4–11; P=0.00).

Fernandez-Menendez et al. [26] showed sensitivities of WBC and CRP of 57% and 79%, respectively and specificities of WBC and CRP of 65% and 55%, respectively for the findings detected in the DMSA.Another study also reported sensitivities of WBC and CRP of 70.1% and 52.4%, respectively, and specificities of WBC and CRP of 61.5% and 77.3%, respectively for the DMSA abnormalities [27]. After adjustment by multivariate analysis, fever and elevated CRP (OR, 1.57; 95% CI, 1–2.3; P=0.01) remained associated with renal scarring in our study.

In this study, after evaluation by multivariate analysis, the predictive factors for abnormal DMSA were detected to be age ≤6 months, fever, and positive laboratory (elevated CRP, elevated WBC, and decreased osmolality). The patients were evaluated not only according to age groups and localization but also according to all the risk factors. Otherwise, many patients may be skipped.

In conclusion, in this study, we demonstrated that the presence of a cortical defect was the main risk factor for VUR in patients with upper UTI. The absence of abnormal US findings in a patient does not eliminate the presence of cortical defects suggestive of pyelonephritis. On the other hand, we showed that rates of cortical defects and VUR were higher than expected in patients with lower UTIs. The findings of the current study suggest that VUR should be evaluated in patients with lower UTIs without renal scarring.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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