

Original article

Clinical Characteristics of Urinary Tract Infections in A Tertiary Center

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ÖZET

Üçüncü basamak sağlık merkezinde üriner sistem enfeksiyonlarının karakteristikleri

Amaç: Bu çalışmanın amacı üriner sistem enfeksiyonlarına (ÜSE) zemin hazırlayan ürolojik anormalliklerin tipini ve sıklığını belirleyerek, ÜSE olan farklı anomalilere sahip hastalarda renal parankimal hasar insidansını araştırmaktır.

Material ve Metot: 2003 ve 2008 yılları arasında Ondokuz Mayıs Üniversitesi Pediatrik Nefroloji Polikliniği'ne ÜSE nedeniyle başvuran hastalar değerlendirildi.

Bulgular: İncelenen 634 hastanın %65,1'i kız; %34,9'u erkekti. Olguların %30,9'unda üst ÜSE mevcuttu. Sekonder vesikoureteral reflüsü (VUR) olan hastalarda karşılaşılan en sık etiyolojik faktör nörojenik mesane ve aşırı aktif mesane idi. Skar oluşumu için 1 yaştan büyük olmak ($P=0,001$, OR 4,57 (95% CI 2,11–9,89) ve VUR olması ($P=0,001$, OR 7,51, 95% CI 4,5-12,5) bağımsız risk faktörleri olarak tespit edildi.

Sonuç: Bu çalışma ÜSE geçiren çocuklarda 1 yaştan büyük ve VUR'e sahip olmanın renal skar gelişimi için prediktif faktörler olduğu ortaya konmuştur. Akut ve rekürren üriner sistem enfeksiyonlarının erken teşhis ve etkin tedavisi ile skarlaşma insidansı azaltılabilir.

Anahtar Kelimeler: Mesane disfonksiyonu; reflü; renal skar; üriner sistem enfeksiyonu; çocuk

ABSTRACT

Objective: The aim of this study is to identify the types and incidence of urological anomalies serving as the causative factors for urinary tract infection (UTI), the incidence of renal parenchymal scarring in different abnormalities of the patients having UTI.

Material and Method: The patients which referred to Pediatric Nephrology outpatient clinic at Ondokuz Mayıs University for UTI between years of 2003 and 2008 were evaluated.

Results: 634 patients were analyzed, %65,1 of the cases were girls and %34,9 were boys. %30,9 of the, patients had upper UTI. The most common etiology in patients with secondary vesicoureteral reflux (VUR) was neurogenic bladder followed by overactive bladder. The age of above 1 year ($P=0.001$, OR 4.57 (95% CI 2.11–9.89) and presence of VUR ($P=0.001$, OR 7.51, 95% CI 4.5-12.5) were found independent factors for scar formation.

Conclusions: This study indicates that age above 1 year and VUR are the most predictive variables for the presence of renal scarring in children presented with UTI. A great effort is needed to reduce the incidence of scarring by early diagnosis and effective early management of acute and recurrent urinary tract infections.

Key Words: Bladder dysfunction; reflux; renal scar; urinary tract infection; children

INTRODUCTION

Urinary tract infections (UTI) are the second most commonly seen infections after respiratory tract infections¹. If the UTI is not diagnosed, investigated and managed appropriately subsequent renal scarring may lead to hypertension, decreased renal function and end stage renal disease²⁻⁶.

Vesicoureteral reflux (VUR) and other urological problems are still the leading underlying causes of chronic kidney disease (CKD) in our country². It is obvious that early diagnosis, treatment and identification of the predisposing factors for scarring will prevent the recurrences and morbidity in cases with UTI^{1,3,4}.

The aim of this study is to investigate the clinical features, the types and frequencies of urologic anomalies paving the way for UTI and their associations with renal scarring.

MATERIAL and METHOD

Medical records of 634 patients with UTI admitted to pediatric nephrology department between 2003 and 2008 in Ondokuz Mayıs University are included in this study.

Patients between the ages of 0-17 with first or recurrent febrile UTI with positive urine culture were included in the study. Patients were accepted as having recurrent UTI if any of the following was present; two or more episodes of UTI with acute pyelonephritis or upper UTI; one episode of UTI with acute pyelonephritis or upper UTI plus one or more UTI with cystitis or lower UTI; three or more episodes of UTI with cystitis or lower UTI⁷. Urine samples were collected by urine bags or by clean-

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catch method in infants and midstream urine in older children. If samples were contaminated then a catheterization or suprapubic sample was taken in infants. UTI was defined as positive pyuria and/or bacteriuria with positive urine culture (At least two consecutive urine culture showed a growth of greater than 100,000 colonies per ml. with one microorganism in clean catch midstream specimens or catheter-collected specimens greater than 10,000 colonies per ml.) in symptomatic patients. Pyelonephritis was defined as body temperature more than 38.5°C, leukocyte count more than 10,000/mm³, erythrocyte sedimentation rate more than 35 mm/h, and a positive urine culture.

Patients were divided into three groups according to their ages: Group I: 0-12 months, Group II: 13-60 months, Group III: more than 60 months

Renal ultrasound was performed in all of the patients. Voiding cystourethrogram was performed in selected patients by using urografin 30% and evaluated for the presence and grade of reflux using international grading system. Grade I-III reflux was defined as low grade while grade IV-V as high. VUR was divided into two groups as primary and secondary VUR. Secondary VUR was defined as the VUR secondary to conditions like bladder dysfunction, double collecting system, posterior urethral valve and bladder diverticuli.

The dimercapto-succinic acid (DMSA) renal scan was performed at least 6 months after UTI. DMSA-scintigraphy was performed two hours after injection of 99m-Tc DMSA taking one posterior oblique images with a gamma camera while patient was in the prone position. Kidney uptake of less than 45% of the total renal activity was considered as abnormal. Renal scar was defined as focal or generalized according to the pattern of diminished radionuclide uptake areas or multifocal perfusion defects. Urodynamic studies were performed by urologists on children with symptoms of bladder dysfunction in the department of Urology.

Statistical analysis

Data were recorded in binary form and statistical analysis was performed with SPSS for Windows® (SPSS Inc., Chicago, IL, USA statistical software). The normality of the distribution of continuous parameters was evaluated by the Kolmogorov-Smirnov test.

Descriptive data which followed normal distribution were expressed as mean $\pm$ standard deviation and those followed non-normal distribution were

expressed as median. Kruskal Wallis test was used when the conditions for parametric tests were not fulfilled. Comparisons of categorical variables were made by chi-square analysis. Logistic regression analysis was performed to evaluate the independent factors for scar formation.

All tests were two-sided with $p < 0.05$ considered as statistically significant.

RESULTS

We have evaluated 634 cases with UTI. The mean age of the patients was 62 ± 51 months. 65.1% ($n=413$) were female and 34.9% were male. UTI was more frequent in boys than girls under one year of age and always more frequent in girls after one year of age ($p = 0.001$). 103 (16.3%) of patients were admitted with first UTI, whereas 531 (83.7%) were admitted with recurrent UTI.

There was upper UTI in 30.9% of patients ($n=438$), and lower UTI in 69.1% of patients ($n=196$). In patients under 1 year of age upper UTI frequency was significantly higher than the other age groups (Table 1) ($p=0.001$).

Table 1. Distribution of Infection Site of Urinary Tract and age Groups

Groups	Lower UTI		Upper UTI		Total	
	n	%	n	%	n	%
Group I	94	54	80	46	174	27.5
Group II	108	69.2	48	30.8	156	24.6
Group III	236	77.6	68	22.4	304	47.9
Total	438	69.1	196	30.9	634	100

*Group I: 0-12 months; Group II: 13-60 months; Group III: more than 60 months

**UTI, urinary tract infection

The most associated urological abnormalities were VUR followed by neurogenic bladder. In patients with VUR, the most common abnormalities were bladder dysfunction and bladder diverticuli. Urologic abnormalities detected in patients with UTI and refluxes are shown in Table 2 and 3 respectively. Voiding cystourethrogram (VCUG) was performed in 416 of cases and VUR was detected in 33% of these. 56% ($n=78$) of patients with VUR had primary VUR whereas 44% ($n=62$) had secondary VUR. The most common etiology in patients with secondary VUR was neurogenic bladder followed by overactive bladder. There was no statistically significant difference between females and males and also between age groups in terms of VUR frequency ($p=0.642$ and $p=0.314$ respectively). VUR frequency was not significantly different between patients with upper UTI and lower UTI ($p=0.731$).

Table 2. Urologic Abnormalities Detected in Patients with UTI

Urologic abnormalities		Cases (n)		Scar	
		n	%	n	%
VUR*	Primer	71	55	40	56.3
	Secondary	59	45	51	86.4
	*Neurogenic Bladder	30	51	28	93.3
	*Overactive Bladder	13	22	10	76.9
	*Low Capacity Bladder	4	7	4	100
	*Double Collecting System	5	8	3	60
	*Posterior Urethral Valve	2	3	2	100
	*Bladder Diverticuli	15	25	14	93.3
	*Low capacity Bladder	4	7	4	100
Bladder Dysfunction	Neurogenic Bladder	20	3.2	13	65
	Overactive Bladder	12	1.9	4	33.3
	Low Capacity Bladder	8	1.3	1	12.5
Nephrolithiasis		8	1.3	5	62.5
Ureterovesical Obstruction		4	0.6	3	75
Ureteropelvic Obstruction		10	1.6	4	40
Multicystic Dysplastic Kidney		8	1.3	1	12.5

* Only patients with voiding cystourethrography were taken account when analyzing the frequency of VUR

**VUR, Vesicoureteral reflux

Table 3. Urologic Abnormalities Detected in Patients with Reflux

Urologic abnormalities	Percentages	
	n	%
Bladder Dysfunction	Neurogenic Bladder	32
	Overactive Bladder	14
	Low capacity bladder	4
Bladder diverticuli	16	11.4
Double Collecting System	5	3.5
Ureteropelvic obstruction	4	2.8
Posterior urethral valve	3	2.1
Simple cyst	2	1.4
Horseshoe kidney	2	1.4
Agensis	2	1.4
Ectopia	1	0.7

Patients with reflux were divided into two groups as having low grade VUR (grade I,II,III) and high grade VUR (grade IV, V). In 213 of ureters with VUR (139 cases) low grade and high grade VUR frequency was 143 (67.1%) and 70 (32.9%) respectively. 50% of patients with secondary VUR had high grade VUR whereas 32.1% of those with primary VUR had high grade VUR ($p=0.031$). Of these patients with high grade VUR in secondary VUR group, 80.8% had neurogenic bladder. High grade VUR was more frequent in males ($\chi^2:4.23$ $p=0.04$).

Dimercaptosuccinic acid (DMSA) radionucleid scintigraphy could be performed in 434 (68.4%) of patients with UTI and scars were detected in 156 (35.9%) of them. In 35 patients with scar, VCUG for VUR evaluation could not be performed due to lack of parental consent. Both VCUG and DMSA could be performed in 348 (54.9%) of patients. There was statistically significant difference in the scar rate between patients <1 year old and >1 year old ($p=0.042$). Scar was seen in 91 (70%) of 130 patients with VUR and 55

(37.7%) of 218 patients without VUR. The frequency of scar was 6.7 times higher in patients with VUR than patients without VUR. ($\chi^2:65$, $P<0.0001$, OR:6.7, CI: 4-10.9). Of these 55 patients without VUR, 5 had bladder dysfunction, 12 had neurogenic bladder whereas no urological anomaly was detected in 25 patients with scar. The urological abnormalities detected in patients with scar are shown in Table 2. Logistic regression analysis revealed that the age of above 1 year ($P=0.001$, OR 4.57 (95% CI 2.11–9.89); presence of VUR ($P=0.001$, OR 7.51, 95% CI 4.5-12.5) were independent factors for scar formation.

The scar frequency was higher in patients with secondary VUR than primary VUR. ($\chi^2: 13.9$ $p=0.001$). There was significant difference in the frequency of scar between patients with high grade VUR and those with low grade VUR. ($\chi^2:16.5$, $p=0.001$). When the 71 patients with primary VUR were evaluated separately, the frequency of scar was higher in patients with high grade VUR than those with low grade VUR ($\chi^2: 7.68$, $p=0.06$).

Table 4. The Frequency and Types of Bladder Dysfunction Detected in Patients with and Without VUR

		Urodynamic results								Total	
		Normal		Overactive bladder		Neurogenic bladder		Low capacity bladder			
		n	%	n	%	n	%	n	%	n	%
Reflux	Present	17	11.6	14	9,9	32	22,3	4	2,8	67	46,8
	Absent	34	23.2	13	9,2	20	14,1	9	6,3	76	53,2
Total		51	34.8	27	19.5	52	36,4	13	9.1	143	100

Table 5. Evaluation of the Relationship Between Bladder Dysfunction and Scar with/without VUR

	Neurogenic Bladder		Overactive Bladder		Low Capacity Bladder		Total
	n	%	n	%	n	%	
Renal Scar Without VUR	11	55	4	20	1	5	16 of 20 cases
Renal Scar with VUR	28	54.9	10	19.6	4	7.8	42 of 51 cases

In 143 (22.5%) patients, urodynamic evaluation was performed. Table 4 shows the frequency and types of bladder dysfunction detected in patients with and without VUR.

In 52 patients with neurogenic bladder, two patients had tethered cord, two patients had Hinman's syndrome and 48 patients had spinal dysraphism.

In urodynamic evaluation, bladder dysfunction other than neurogenic bladder was observed in 12.9% of patients with vesicoureteral reflux and 8% of non-VUR cases ($p=0.976$). Table 5 shows the relationship between scar, VUR and bladder dysfunction.

31 patient (4.9%) had decreased estimated glomerular filtration rate at presentation. 10 (%32.2) had stage II, 14 (%45.2) had stage III, 5 (%16.1) had stage IV and 2 (%6.5) had stage V chronic kidney disease according to National Kidney Foundation's Kidney Disease Outcomes Quality Initiative classification.

DISCUSSION

All the patients reported in this study are referrals because of first or recurrent UTI during a four-year period. In the present study %27.8 of patients were under 1 year of age and boys accounted for %72.7 of UTIs in this age group with a decreasing ratio as the age increases.

Other studies have reported similar conclusions, with some of the male risk of UTIs hypothesized as being attributable to the uncircumcised state⁸⁻¹⁰. Similarly, none of our patients under age of 1 year was circumcised. The lack of circumcised patient group made it impossible for us to identify the impact of circumcision on the development of UTI. %45.5 of patients less than 1 year of age had upper UTI whereas upper UTI frequency decreased significantly with increasing age. In the present study, 16.3% of patients referred to our

clinic had first UTI whereas 83.7% had recurrent UTI. This finding can be explained by the status of our center being a tertiary center and patients with first UTI are generally treated in primary or secondary care settings in our region.

The most common urological abnormality for UTI risk is reported to be VUR ranging from 7% to 85% according to American Academy of Pediatrics¹¹ Hansson S et al found that frequency of VUR was 26% among UTI patients¹². In another study from Turkey, VUR frequency in UTI patients was found 24.8% and female predominance was noticed¹³. We also found that VUR is the most common abnormality in our patients (21.9%) followed by neurogenic bladder. Treatment strategies are based upon the currently available literature, according to presence of renal scarring and its grade, spontaneous resolution of VUR, the presence of voiding dysfunction, age of the patient, and family preference. Prior to surgical intervention for VUR, patients with voiding dysfunction treated adequately. Children over five years of age or who did not respond to medical therapy or had high grade reflux with scarring were recommended surgical correction.

In our study, we found no statistical differences among gender and age groups but male predominance in infants. VUR in children can be classified as primary, or secondary. 65.6% of 634 patients in whom VCUG could be done %44.3 had secondary VUR and 51.6 % of these had neurogenic bladder. 61.5% of all patients with neurogenic bladder had VUR. Although 92.3% of these patients had spinal dysraphism as a cause of neurogenic bladder, most of these patients were neither investigated nor treated for the neurogenic bladder before their admission to our clinic because of UTI. This can be due to the lack of awareness of the condition amongst physicians. We think that more caution should be given in the

care of patients with spinal dysraphism by clinicians.

There is a controversy regarding the association between VUR and renal cortical scarring. VUR is thought to predispose the child with UTI to pyelonephritis and renal scarring by the active transport of microbes from the urinary bladder to the kidneys but a causal connection between VUR alone and renal scarring has not been fully established¹⁴⁻¹⁷. Some of the previous studies established a strong association between VUR, UTI, and renal cortical scarring¹⁸⁻²⁰.

Recently, Oh et al reported that VUR is the common risk factor for acute scintigraphic lesion and ultimate scar formation¹⁸. It is also reported that a high-grade form of VUR is more closely associated with renal scars than low grade^{5,21}.

However, several prospective studies using DMSA scintigraphy have demonstrated that acute renal changes can occur in the absence of VUR and showed a comparable risk for pyelonephritic scars between patients with VUR and without VUR^{5,22}. A meta-analysis concluded that primary VUR is neither sufficient on its own, nor it is essential for the development of renal damage in the presence of a UTI²³. In our study, DMSA could be performed in 434 (68.5%) of 634 patients and scarring was detected in 35.9% of these. 62.8 % of scarred kidneys were associated with VUR and patients with VUR were more prone to renal scarring with a 6.7 times higher risk compared to those without VUR. Also logistic regression analysis revealed that the presence of VUR was an independent risk factor for scar formation. There are also conflicting reports regarding the association between reflux grade and frequency of scar formation. Several reports showed a strong relationship between abnormality on DMSA scan and VUR severity whereas the others did not confirm this²⁴⁻²⁷. Silva et al reported that all subtypes of renal damage were associated with high-grade reflux²⁸. A recent study from Turkey reported that male gender, age over 27 months at presentation in girls and high grade reflux in both genders correlated with the presence of renal scar at presentation²⁶. However Ditchfield et al indicated that there was no association between the severity of VUR and persistent renal cortical defects²⁹. Our study demonstrated that high grade VUR is associated with an increased incidence of scarring in both patients with primary and secondary VUR. When we compared the frequency of scarring between primary and secondary VUR, we observed that patients with secondary VUR were more prone to renal scarring than those with primary VUR. In patients with neurogenic bladder

with increased risk for vesicoureteric reflux, over-distention of the bladder, high pressure voiding, large post-void residuals increase the susceptibility to recurrent UTI and new scars³⁰.

Perhaps the incompletely effective treatment or therapeutic delay time during the acute pyelonephritis attack can be an important risk factor for subsequent renal scarring in acute pyelonephritis. Since this is a retrospective study and 83.7% of the patients referred to us had recurrent UTI and had been treated in various hospitals previously, we can not draw a certain conclusion whether renal scarring is associated with recurrent UTI attacks or VUR itself. We did not find any predisposing factor in 25 patients with renal scar. The absence of VUR in some children with renal scar can be explained by the imperfect sensitivity of VCUG for detecting VUR or the intermittent nature of the VUR or its spontaneous resolution with time. Also, undiagnosed or recurrent pyelonephritic attacks may have resulted in such scars in these patients.

Several reports indicated that acute pyelonephritis during infancy causes much more renal scar risk due to the unique kidney papillary morphology at this age^{31,32}. However, other studies did not confirm that younger children are at a greater risk for renal scarring^{33,34}. In our study we observed a significant difference in the scar frequency between patients under 1 year of age and above 1 year of age. Furthermore, logistic regression analysis indicated that being above age 1 year is an independent risk factor for scar formation. Soyulu et al reported that age at diagnosis >27 months was found to be a cut-off value among the girls for predicting renal scarring²⁶. Another study from Turkey showed that the scar rate was higher in patients with pyelonephritis and recurrent afebrile UTI when compared to those with first afebrile UTI. Also, in that study mean age of the children with recurrent afebrile UTI was higher than in the other two groups¹³. In the present study not only children with first UTI but also with recurrent infection were evaluated. In our study, higher scar rate in patients with older age at presentation could be explained by the unawareness or under-evaluation of previous UTIs and this finding may indicate that renal scarring is associated with recurrent UTI episodes.

Functional voiding disorders in recurrent UTI are not uncommon, but often overlooked in children. Several studies of children with UTI have reported the association of recurrent UTI with functional voiding disorders^{35,36}. We have performed urodynamic evaluation in 143 patients.

16 patients with bladder dysfunction without VUR, had renal scarring indicating the importance of evaluating the bladder function in recurrent UTIs without VUR (Table 6). Since voiding dysfunction in children with recurrent UTI and/or reflux is a medically treatable condition, children with recurrent UTI should be strictly questioned for persistent symptoms of voiding dysfunction such as urgency, frequency, squatting behavior and diurnal incontinence.

The present study has several limitations. First, the data are retrospective and therefore there are some missing radiologic evaluations. Second, since VCUG could not be done in all patients, we might have missed VUR in patients only underwent renal ultrasound. Third, this is not a longitudinal study; therefore we could not

evaluate the new or progressive scar formation in these patients.

In summary, the results of this study indicate that age above 1 year and VUR are the most predictive variables for the presence of renal scarring in children presented with UTI. On the other hand, since scarring can develop in kidneys without VUR, patients with first or recurrent UTI should be evaluated carefully even if they had no VUR. We also want to emphasize the importance of addressing functional voiding dysfunction in children both with VUR and without VUR. A great effort is needed to reduce the incidence of scarring by early diagnosis and effective early management of acute and recurrent urinary tract infections.

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