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The Incidence of Renal Scarring and its Related Factors in Children with First Pyelonephritis

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Introduction: Urinary tract infection (UTI) is common in children. UTIs are important in view of the morbidity and risk of scarring. Several factors have been reported to be responsible for progression to scarring. The aim of this study was to determine the incidence of scar and its related factors.
Materials and Methods: In this study, 26 males and 77 females (3 months - 12 years) with first pyelonephritis were evaluated. All patients underwent ultrasound, cystourethrography, and Dimercaptosuccinic acid scan. A follow-up scan was performed 6 months later. Age, gender, organism, presence, and grade of vesicoureteral reflux (VUR), delay in treatment, total white blood cell counts (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels on admission were recorded. Logistic regression analysis was used to evaluate the association between the variables and scar.
Results: Of 103 patients, 47.6% had VUR. Scar was detected in 38.8%. There were significant associations between delay in treatment (p=0.0001), grade of VUR (p=0.03) and elevated ESR (p= 0.006), CRP (p=0.002) and WBC (p=o.oo5) with scar. No association was established with age, sex, VUR, and organism. On multivariate analysis, delay in treatment was independently associated with scar.
Conclusions: We found that the grade of VUR, delay in treatment, and increased ESR, CRP and WBC were important factors related to scar.

Keywords: Child; Pyelonephritis; Renal Scar.

Running Title: Renal Scarring in Pyelonephritis

Introduction

Urinary tract infection (UTI) is common in children. By the age of seven, 8.4% of girls and 1.7% of boys suffer at least one episode of UTI [1]. UTIs are important in view of their acute morbidity and long-term risk of renal scarring. The renal scar can result in hypertension, chronic renal failure, and complication during pregnancy [2]. The ultimate goal for the care of children with UTI is to prevent permanent renal damage. Several factors have been reported to be responsible for progression to renal scarring including age at presentation, gender, delay in adequate antibiotic treatment, presence of urinary anomalies and vesicoureteral reflux (VUR), bacterial virulence, recurrent infection, host immunologic and inflammatory reactions, and genetic susceptibility [2-3]. However, the results of various studies on the risk factors of renal scarring are not conclusive and in recent years, the role of some of these predisposing factors of renal scarring with pyelonephritis has been questioned. Of particular interest is VUR that until recently was thought to be the most important risk factor for scar formation. A Meta- analysis showed that VUR was a weak predictor of renal damage in children with UTI [4].

The aim of this study was to determine the incidence of renal scarring and its related factors in children with first pyelonephritis.

Materials and Methods

This prospective (longitudinal) study was conducted from March 2008 to November 2010. (at Mousavi Hospital in Zanjan, a city in the northwest of Iran). A total of 103 children (26 males and 77 females) aged between 3 months and 12 years following their first documented pyelonephritis were enrolled. The study was approved by the ethics committee and informed consent was obtained from the parents.

Pyelonephritis was defined as any bacterial growth in urine obtained by suprapubic aspiration, the growth of $>10^4$ Colony-Forming Units (CFUs) per mL of a single pathogen in specimens obtained by transuretheral catheterization, or the growth of $>10^5$ CFUs/ mL of a single species in two consecutive urine obtained by bag or mid-stream in a symptomatic child, along with a temperature of 38.5°C or more, leukocytosis or elevated C-reactive protein (CRP).

All patients were treated with intravenous antibiotics (ampicillin + aminoglycoside or a third-generation cephalosporin) for at least 48 hours after the fever subsided, followed by oral antibiotics for 7 to 14 days. Prophylactic antibiotics were also administered. All children underwent renal ultrasound examination on admission. DMSA (dimercaptosuccinic acid) scan was performed in all patients during the first week of admission. Acute pyelonephritis was defined as single or multiple areas of diminished uptake of DMSA with preservation of the renal contour. A follow-up DMSA renal scan was performed 6 months after the first study. Scar was defined as persistent changes in the same location as in the first DMSA scan. Voiding cystourethrography (VCUG) was performed in all patients using the standard method between 2 - 6 weeks after the diagnosis of acute pyelonephritis or once the infection was controlled. Voiding cystourethrography (VUR) was classified according to the International Reflux Study Group [5]. Exclusion criteria were a normal first DMSA renal scan, a positive history of previous pyelonephritis, recurrent urinary infection during follow-up periods, shrunken kidney or diffuse reduction of the size and function on the first DMSA scan, urinary tract anomalies other than primary VUR (cystic disease, obstruction, secondary VUR, duplication, bladder anomalies, etc) and impaired renal function.

The children were categorized into three different age groups (<1 yr, 1-5 yrs, >5 yrs). The following data were recorded for each patient: age, gender, infective organism, presence and grade of VUR, delay in treatment (days from the onset of symptoms to initiation of antibiotics therapy), total white blood cell count, and the levels of ESR (erythrocyte sedimentation rate) and CRP on admission. The sample size was calculated assuming P=0.5, d=0.1 and a significance level of 5% using the formula for descriptive studies. Values were expressed as number (percentage), and comparisons were performed by chi-square test for categorical variables. A logistic regression model was constructed to examine the association between scar formation and the relevant variables. All statistical analyses were performed using the SPSS 16 computer software program for Windows (SPSS, Chicago, IL, USA).

Results

In total, 103 children with first documented pyelonephritis were included in the analysis. All patients had acute abnormal renal scanning. The characteristics of the patients are summarized in Table 1.

Table1. Demographic and clinical characteristics of children with pyelonephritis

variables	n (%)
Sex	
Male	26(25.2)
female	77(74.8)
Age (yr)	
<1	45 (43.7)
1-5	39 (37.9)
>5	19 (18.4)
VUR	
Present	49(47.6)
Absent	54(52.4)
Grade of VUR	
I-II	15(30.6)
III	21(42.8)
IV-V	13(26.5)

During follow-up, 38.8% (n=40) had a renal scar on the second DMSA scan which was performed after six months. All renal scars occurred at the sites corresponding to those of the acute pyelonephritis lesions seen on the initial scan.

The risk of renal scarring following acute pyelonephritis according to gender, age groups, delay in treatment, VUR and grade of VUR and lab finding is shown in Table 2.

Table 2. Relative risk and 95% CI of renal scarring within 6 months following pyelonephritis by study variables in univariate analysis

Variables	Follow-up DMSA scan		P value	RR	CI
	Normal n (%)	Scar n (%)			
Sex					
Male	15 (57.7)	11 (42.3)	0.67	1	
female	48 (62.3)	29 (37.7)		0.82	0.33-2.04
Age (yr)					
<1	25 (55.6)	20 (44.4)	0.21	1	
1-5	28 (71.8)	11 (28.2)		0.49	0.20-1.22
>5	10 (52.6)	9 (47.4)		1.13	0.38-3.30
Delay in treatment					
<2 day	38 (86.4)	6 (13.6)	0.001	1	
2-6 "	19 (61.3)	12 (38.7)		4	1.30-12.31
>6 "	4 (15.4)	22 (84.6)		34.83	8.85-137.
VUR					
Present	27 (55.1)	22 (44.9)	0.22	1	
Absent	36 (66.7)	18 (33.3)		0.61	0.28-1.36
Grade of VUR					
I-II	11 (73.3)	4 (26.6)	o.o3	1	
III	13 (62)	8 (38)		1.67	0.39-7.21
IV-V	3 (23.1)	10 (76.9)		8.33	1.47-47.33
Organism					
E-coli Non	41 (64.1)	23 (35.9)	o.21	1	
E-coli	7 (46.7)	8 (53.3)		2.04	0.65-6.34
ESR(mm/hr)					
<50	46 (70.8)	19 (29.2)	o.oo6	1	
≥50	17 (43.2)	21 (56.8)		3.18	1.37-7.37
CRP(mg/l)					
<10	24 (80)	6 (20)	0.002	1	
10-20	32 (62.7)	19 (37.3)		2.38	0.82-6.85
>20	6 (30)	14 (70)		9.33	2.52-34.58
WBC (/mm³)					
10000-15000	40 (75)	14 (25)	0.005	1	1.40-7.59
>15000	23 (47.9)	26 (52.1)		3.26	

RR: Relative risk CI: Confidence interval%95

Delay in treatment, grade of VUR, elevated levels of ESR, CRP and WBC were significantly associated with the renal scar. The relative risk and 95% confidence interval of all factors are shown in Table 2. These findings showed that the risk of renal scarring increased with the delay in treatment, grade of VUR and elevated ESR, CRP and WBC. In multivariate analysis, the delay in treatment was independently associated with scar formation after controlling other variables (Table3).

Table3. Relative risk and 95% CI of renal scarring within 6 months following pyelonephritis by study variables in multivariate analysis

Variables	RR	CI
Sex		
Male	1	
female	0.73	**0.18-3.01**
Age (yr)		
<1	1	
1-5	0.63	**0.16-2.46**
>5	2.05	**0.40-10.36**
Delay in treatment (day)		
<2	1	**1.20-16.84**
2-6	4.50	**8.04-176.18**
>6	37.65	
ESR(mm/hr)		
<50	1	
≥50	1.78	**0.47-6.77**
CRP(mg/l)		
<10	1	
10-20	1.65	**0.38-7.10**
>20	3.41	**0.55-21.22**
WBC(/mm³)	1	
10000-15000	1.40	**0.38-5.01**
>15000		

RR: Relative risk CI: Confidence interval%95

Discussion

In this study, we evaluated the incidence and some related factors of post pyelonephritic renal scarring in children. The study showed the incidence of renal scarring was 38.8%. Delay in treatment, grade of VUR and elevated ESR, CRP and WBC were risk factors of renal scarring after acute pyelonephritis in children. The incidence of renal scar formation in our study was 38.8% which is in agreement with those reported by other studies [6-7]. In our study, we found no significant relationship between gender and the risk of scar formation. A study revealed that the

male gender was a significant risk factor for scarring [8] while no gender differences have been observed in other studies, which supports our finding [9-12].

The general belief is that infants seem to be more susceptible to renal injury and acquired scaring. The young growing kidney is susceptible to insults because of the unique kidney papillary morphology at this age [13]. On the other hand, recognition and treatment of pyelonephritis is often delayed within the first years of life. Some studies have shown that scar formation is associated with age less than 2 years [14]. Recent studies have not confirmed the conventional view that the risk of renal scarring after pyelonephritis diminishes with age. In many studies, renal scar formation has been reported to be more in older children [10-11, 15-17]. While some other studies have reported no significant difference in the rate of scarring with age [6,12,18]. This is in accordance with our results. It is more likely that all children bear the risk of renal scaring in cases of acute pyelonephritis. In our study, renal scarring was associated with the delay in the treatment of acute pyelonephritis, and we found that a progressive delay in antibiotic treatment (more than 2 days) was associated with a significant increase in the risk of scar formation. This is in agreement with the results of other studies that reported early aggressive therapy of acute pyelonephritis in children reduces the frequency and degree of scarring [2,12,19-21]. More recently, some authors stated that early antibiotic treatment was not effective in reducing subsequent renal damage [6,22] suggesting that once acute pyelonephritis has occurred, ultimate renal scarring is independent of the timing of therapy. The American Academy of Pediatrics recommendation for febrile infants and children with suspected or proven UTI is early antibiotic treatment [23]. VUR is a risk factor that was thought to be the most important for renal scar formation until recently. In our study, the proportion of scar formation was not different for those with and without VUR. Similar results have been reported by other studies [4,17,22,24]. However, the results of several studies indicate that VUR is a predictive factor for post pyelonephritic scar [8-12,16,20,25]. Moreover, the results of various studies on the role of the grade of VUR as a risk factor for scar are not consistent. No association has been found in some studies between the reflux grade and scar formation [16,20,26-27].

Similar to our study, some reports have suggested that more severe grades of VUR are better predictors of renal scar than minor grades [8,12,15].

It seems that renal scarring is probably due to multifactorial causes. Perhaps different anatomical structure of the papillae protects the kidney or some kidneys might be protected by genetic or environmental factors that modify the degree of renal parenchymal inflammation [4].

Considering lab findings, our study revealed a significant association between scar formation and elevated ESR, CRP and WBC on admission. Most of the studies have shown such a correlation [12,16,24,28-29]. CRP is an acute phase protein in humans, and its concentration rapidly increases in response to infection, trauma, and inflammation. The white blood cells count represents the inflammatory status. Toxic metabolites released from infiltrating leukocytes have been reported to damage the renal tissue [2]. In some researches, no association has been found between scar formation and elevated ESR, CRP and WBC at the time of infection [9,18,20].

The importance of bacterial virulence in the development of scar is unclear. Orellana et al. reported that children infected with non-Ecoli organisms had significantly more permanent renal damage than those infected with E-coli[10]. However, in other studies including ours, no association was established between renal damage and the infective organism [29-30].

Conclusions

In our study, renal scarring occurred only in some children with first febrile UTI (38.8%). We found that the grade of VUR, delay in treatment, and elevated ESR, CRP and WBC were important related factors for renal scarring. Multivariate analysis showed that delay in treatment was independently associated with scar formation. There is controversy regarding risk factors for scarring in the literatures. We recommend further research to evaluate the role of genetics, host defense mechanisms, and immunologic factors.

Limitations: Although we tried to select children with first UTI using clinical findings and DMSA renal scan, there may be some children with previous UTI without any symptoms and a normal scan.

Conflict of Interest

There is no conflict of interest related to the material in the manuscript.

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