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Risk Factors of Acute Renal Cortical Lesions in Scintigraphy in Children with Urinary Tract Infection

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Introduction: Urinary Tract Infection (UTI) is one of the most common pediatric infections. UTI may create cystitis or pyelonephritis by involving bladder or renal parenchyma, respectively. Pyelonephritis, especially in pediatric patients, can lead to scar formation in kidneys and consequent complications such as hypertension, proteinuria, dysfunction and chronic renal insufficiency. The current study aimed to determine risk factors of acute rental cortical lesions in renal scintigraphy in children with UTI.
Materials and Methods: Fifty-three patients with significant renal cortical lesions and 53 cases without significant renal cortical lesions were compared based on the intensity of findings of DMSA scintigraphy within the first two weeks of diagnosis. Patients were divided into three groups of 1 month to 2 years, 2 to 4 years and 4 to 10 years.
Results: Of 106 patients, 11 males (20.8%) and 42 females (79.2%) had significant acute renal cortical lesions, whereas 15.1% of males and 84.9% of females had no significant acute renal cortical lesions. There was a significant difference in the degree of fever, the average interval between the onset of fever and treatment, mean level of CRP, leukocytosis and ESR in the two studied groups. The presence of Vesicoureteral Reflux (VUR), low initial hemoglobin and low initial BMI as random findings were associated with significant renal cortical lesions. Gender, age, grade of VUR and type of organism in urine culture had no significant association with significant renal cortical lesions.
Conclusions: In this study, delaying in treatment, high degree fever, leukocytosis, high initial ESR and CRP, existence of VUR and low initial BMI and hemoglobin levels were associated with an increase in the value of acute renal cortical lesions, so in these cases, DMSA scan is suggested.

Keywords: Urinary Tract Infections; DMSA (Dimercaptosuccinic Acid); Renal scars; Pediatrics.

Running Title: Renal Cortical Lesions in Scintigraphy in UTI

Introduction

Acute pyelonephritis may lead to scar formation in kidneys and complications such as hypertension, proteinuria, decreasing renal function and chronic renal failure [1]. Changes in

renal cortex created after UTI can be measured by Dimercaptosuccinic Acid Tc99m (DMSA) scan [2], which is considered as the gold standard diagnostic method for renal parenchymal damage [3]. According to studies, the best time to assess the inflammation caused by pyelonephritis through DMSA scan is the first two weeks of UTI diagnosis [3]. Some studies have been performed on identification of predictive factors of scarring in kidneys of children with UTI in which gender, age, leukocytosis, levels of C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), recurrent UTI, Vesicoureteral Reflux (VUR) and its intensity were investigated and contradictory results were obtained [4-11].

Prevention of renal scar in normal kidneys and spread of previous scars are the main objectives of all treatments in childhood UTI. Therefore, children at high risk of renal scar should be identified as soon as possible and undergo appropriate diagnostic and therapeutic measures. The aim of this study was to recognize risk factors in creation of acute renal cortical lesions.

Materials and Methods

Children aged 1 month and 10 years admitted in Urmia Motahari Hospital with the first febrile UTI during May and October 2014 were studied. Inclusion and exclusion criteria are indicated in following list:

Inclusion criteria

- Suspicious clinical signs of UTI
- Fever above 38°C axillary
- Urine analysis with WBC> 5HPF
- Urine culture with a bacteria strain CFU>10^5
- Children aged 1 month to 10 years old

Exclusion criteria

- Urine culture with more than one bacteria strain
- Known congenital hydronephrosis
- Known neurogenic bladder
- History of urinary tract obstruction
- Presence of stone >5mm in the urinary system
- Structural anomalies of genitourinary system expected for VUR
- Previous scar in DMSA

Urine sample was collected based on children's cooperation in two methods of mid-stream and urine bag before starting antibiotic therapy. Blood sampling was performed to investigate initial quantitative CBC, ESR and CRP during the first 24 hours of diagnosis and all samples were analyzed in the central laboratory of Motahari Hospital. Their vital signs, weight and height were measured and DMSA scan was performed within the first two weeks of diagnosis of pyelonephritis. Of patients in the two groups, 53 subjects with significant renal lesions based on the results of DMSA scan and 53 cases with non-significant renal lesions were selected and compared. Patients were divided into three groups of 1 month to 2 years, 2 to 4 years, and 4 to 10 years and ultrasound of kidneys and urinary tract, Direct Radio Nuclide Cystography (DRC) or Voiding Cystourethrogram (VCUG) were performed to detect Vesicoureteral Reflux (VUR).

The intensity of renal cortical lesions was divided based on the results of DMSA according to the areas of reducing absorption in inflammation and destructing parenchyma in scars [5]. Renal parenchymal lesion based on DMSA finding was graded as follows: grade I (equivocal), grade II (single defect), grade III (more than 2 defects), grade IV (contracted or small size kidney) and grade V (no visualization of kidney).

Degrees 1 and 2 considered as non-significant lesions and degrees, 3, 4 and 5 as significant renal lesions [6]. Presence of renal cortical lesions on DMSA scan and its intensity was reported by nuclear medicine specialist and approved by a pediatric nephrologist.

Comparisons of categorical variables were performed by chi-square and fisher exact tests.

Data analysis was performed using SPSS software version 20 (SPSS Inc., IMB Corporation, Chicago, Illinois, USA) and P value below 0.05 considered as statistically significant.

Results

106 children were examined in this study consisting 53 patients with significant renal cortical scars and 53 without significant renal scars (demographic and variables data are shown in Tables 1 and 2).

According to statistical Chi-square test, there were no significant differences in gender (P=0.3) and age (P=0.31) and the presence or absence of significant cortical lesions. There were significant differences in BMI (P value= 0.02), WBC (P=0.0001) and percentiles of hemoglobin (P=0.001) of children in the two studied groups (Tables 2 and 3).

There was no significant difference in the type of organism (P=0.3).

According to Fisher Exact Test, there was a significant difference in the presence of vesicoureteral Reflux (P=0.0001), but not in the severity of VUR (P=0.55) in children with significant and non-significant renal cortical lesions.

According to T-test, significant differences found in the degree of fever (P=0.0001) intervals of the onset of fever and treatment (P=0.007), mean ESR (0.0001) and CRP (0.008) in the two studied groups.

Table 1. Comparison of clinical and paraclinical data according to the presence of significant renal cortical lesions

Variables	Follow-up DMSA scan		P value	RR	CI
	Significant lesions n(%)	Non-significant lesions n(%)			
Sex			0.3		
Male	11(57.8)	8(42.2)		0.679	0.249-1.8517
Female	42(48.2)	45(51.8)		1	
Age(y)			0.31		
1 month-2 y	29(54.8)	23(43.4)		1.996	0.806-4.942
2-4 y	12(22.6)	11(20.8)		1.72	0.580-5.14
4-10 y	12(22.6)	19(35.8)		1	
VUR			0.0001		
Present	20(37.7)	6(11.3)		1	
Absent	33(62.3)	47(88.7)		4.747	1.72-13.102
Grade of VUR			0.55		
I-II	10(38.5)	2(7.7)		1.57	0.178-13.86
III	6(23.1)	2(7.7)		2.75	0.284-26.607
IV-V	4(15.4)	2(7.7)		1	
Organism			0.3		
Non E-coli	3(5.7)	1(1.9)		3.12	0.314-31.002
E-coli	50(94.3)	52(98.1)		1	
BMI(W /L²)			0.02		
<5%	7(13.2)	0		1	
5-85%	38(71.7)	44(83)		1.02	0.366-2.93
>85%	8(15.1)	9(17)		1.125	
WBC(/mm³)			0.0001		
<15000	28(52.8)	46(86.8)		5.74	2.194-15.017
>15000	25(47.2)	7(13.2)		1	
Hb			0.001		
<3%	4(7.5)	10(18.9)		0.4	0.125-1.275
3-10%	24(45.3)	35(66)		0.68	0.408-1.153
10-50%	3(5.7)	0		1.615E9	
50-90%	22(41.5)	6(11.3)		3.667	1.487-9.043
>90%	0	2(3.8)		**1**	

Discussion

In our study, age, gender, initial BMI, leukocytosis, ESR, initial qualitative CRP, interval between the onset of fever and treatment, type of organisms from urine culture, Vesicoureteral Reflux (VUR) and its degree were examined in the two

independent groups with significant and non-significant acute renal cortical lesions in febrile children aged 1 month to 10 years with UTI.

Table 2. Comparison of mean ESR, CRP, delay in treatment and fever according to the presence of renal cortical lesions

Variable	Significant cortical lesions		p-value	CI
	present	absent		
Mean CRP level	38.94	26.77	0.0001	**3.296- 21.043**
Mean ESR level	48.28	25.41	0.008	**13.682-32.845**
Delay in treatment (days)	4.96	3.33	0.007	**0.444- 2.811**
Mean degree of fever(c)	38.97	38.19	0.0001	**0.521-0.968**

The variables associated with renal scars are age and BMI based on logistic regression exam -Step 2[a] - (table 3)

Table 3. Variables in Logistic Regression Exam

Type of Regression	Factors	P value	95% CI	
			Lower	Upper
Logistic regression exam (Step 2[a])	Age	0.011	0.638	0.943
	BMI	0.005	1.008	1.048

this age, due to non-specific symptoms of UTI and delay in the diagnosis and treatment, the rate of renal involvement increases [7], which has been approved in the studies by Ditchfield and Bairaghdar [5, 12]. In our study, most children aged 1 month to 2 years and the maximum rate of significant acute renal cortical lesions was observed in the same group, while there was no statistically significant difference between age and development of acute renal cortical lesions, which was consistent with the results of Ehsanipour study [7]. In some studies, the incidence of renal scar is increased by increasing age [9 and 11]. In general, UTI is more common at all ages except for females aged less than one year. At ages below one year, most cases of UTI are males, which are caused by anatomical abnormalities and not performing circumcision [13-18]. In our study, most children (82.1%) were female, which was consistent with the studies by Ehsanipour and Falakalaflaki [2, 7], while in other studies [10, 11], males constituted most patients with UTI because most study patients aged below one year old. In our study, there was no statistically significant difference between gender and significant renal cortical lesions. This was consistent with the results of studies by Taskinen, Ditchfield and Snodgrass [9, 11, 12]; however, in the study conducted by Mi Oh, the highest rate of renal lesions was observed in male [8]. Few studies have been conducted on the association between initial BMI and malnutrition with development of UTI and renal lesions in children, in which malnutrition has been introduced as a factor reducing the size of kidney and increasing the rate of UTI incidence [13- 20]. In our study, low initial BMI has been associated with creation of significant acute renal cortical lesions based on the percentile of age and gender (P=0.02) (Tables 2 and 3). According to the study by Ditchfield, in cases of high degree fever, renal involvement is about ten times more [16]. In this study, the degree of fever has been significantly higher in the group with significant acute renal cortical lesions (P=0.001), while this case has been rejected in the study by Ehsanipour [2]. In most current studies, the average interval between the onset of fever and treatment has been reported to increase renal cortical lesions [2, 8,10], and in our study, this factor was significantly associated with increased renal cortical lesions (P=0.007). In leukocytosis and neutrophil-mediated release of toxic

Development of significant acute renal cortical lesions is more probable in young infants because of the specific anatomy of the kidney; however at

metabolites from leukocytes and destruction of kidney tissue, the incidence of renal lesions is increased, which is consistent with our study (P=0.001), Falakalaflaki, and Mi oh [7, 8], while this was not confirmed in the study by Ehsanipour [2]. In the present study, ESR and CRP levels were significantly high in the group with significant rental lesions (P=0.0001, CRP) and (P=0.008, ESR), which was consistent with the results of Falakalaflaki and Taskinen studies [7 and 11]. However, in the study by Mi oh, in many cases of UTI, CRP level (Increased Acute-phase protein in inflammation, trauma and infection) is normal even despite significant cortical lesions, but it can be useful in diagnosis and response to treatment [8]. There are few studies on the association between low level of initial hemoglobin, incidence of UTI and renal involvement. In chronic kidney disease, anemia can occur, which is normocytic in most cases and whose predominant mechanism is to decline the production of erythropoietin [14]. In the study conducted on patients with UTI and malnutrition in Pakistan, microcytic-hypochromic anemia (in most cases, Iron deficiency anemia) has also been reported at the same time [20]. In our study, the level of initial hemoglobin was evaluated as a random result based on the percentile for age and sex, in which there was a low association between UTI and initial hemoglobin. Therefore, the low level of initial hemoglobin (due to anemia from iron deficiency as the most common cause of anemia in this age group [19] or other mechanisms) is one of the predisposing factors of UTI and renal lesions; however, proving the existence of this association and its cause requires more studies. E. coli is the most common cause of UTI [13]; however, its role is not completely clear in increasing renal lesions compared to other pathogens (Proteus, Klebsiella, etc.). In our study, in accordance with the study by Falakalaflaki, *E. coli* was the most common cause, while it did not increase the risk of rental lesions; however, in some studies [2, 17], Non-E. coli cases associated with increased risk of scar formation. Vesicoureteral Reflux (VUR) [12] makes kidney exposed to bacteria and thus, more destruction; on the other hand, most cases of UTI are observed in children without VUR [3,7,10, 11,12]. In most studies, VUR was associated with increased risk of renal cortical lesions [2, 3, 8, 9, 10], while in the study by Falakolaflaki, this factor did not have a role [7]. In general, in the present study, 26.6% of the studied individuals had VUR; however, this factor has been significantly involved in the increase of acute renal cortical lesions (P=0.0001). Therefore, it can be said that VUR is an important factor in the development of renal lesions, but it is not the necessary factor for its development [3]. In most studies, the high grade of VUR has been reported as a risk factor for increased risk of renal cortical lesions [2, 3, 5, and 7]. In other studies [8, 12, 14], along with this study, the intensity of VUR had no statistically significant difference between the two groups (P=0.5), which may be due to the small number of children with VUR in the study samples. With the diagnosis of acute significant renal lesions and its treatment in some cases of UTI, the incidence of permanent scar in kidney and its long-time complications can be prevented [21]. The limitations of this study were:

1. the association between the severity of VUR and acute renal cortical lesions was not judicable due to the small number of cases of vesicoureteral reflux.
2. An important factor associated with UTI and renal lesions, voiding dysfunction, was not studied because of not accessing urodynamic studies.
3. Tthere is no method to diagnose unknown previous UTI and anomaly with scared renal parenchyma during fetal period.

Conclusions

In this study, high degree of fever, leukocytosis, delay in treatment, high initial quantitative ESR and CRP levels, and low initial BMI and hemoglobin levels (affected with any causes) were associated with an increase in the value of acute renal cortical lesions, in which DMSA scan is suggested.

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Conflict of Interest

None declared

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