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The evaluation of the relationship of clinical and laboratory evidence with renal damage in the pediatric patients that had urinary tract infections

İdrar yolu enfeksiyonu geçiren çocuk hastalarda klinik ve laboratuvar kanıtların böbrek hasarı ile ilişkisinin değerlendirilmesi

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Abstract

Purpose: Urinary tract infection (UTI) is one of the important infectious diseases of childhood age. It causes serious late-term complications by leading to development of renal scarring in some pediatric patients. In the present study, it was aimed to determine the risk factors in development of renal damage in the pediatric patients that admitted with clinical of acute pyelonephritis.

Materials and methods: In our study, the medical files of the patients were admitted to the pediatric nephrology polyclinic of Pamukkale University Medical Faculty and followed-up with the diagnosis of urinary tract infection were retrospectively evaluated. The study included 197 patients diagnosed with acute pyelonephritis (confirmed by urine culture and clinical evidence) and undergoing dimercaptosuccinic acid (DMSA) scintigraphic imaging. The clinical evidence (fever, recurrent UTI, voiding dysfunction etc.), laboratory evidence (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, polymorphonuclear leukocyte (PNL) count, mean platelet volume (MPV), platelet count, serum urea and creatinine levels) and imaging evidence (urinary tract system ultrasonography (USG), voiding cystourethrography (VCUG) and DMSA scintigraphy) of the patients detected at admission and obtained by anamnesis were evaluated.

Results: The number of the female patients (n=153) was found significantly higher than number of the male patients (n=44) (p<0.001). It was detected that pretreatment fever of 38ºC and over, persisting clinical evidence for 2 days or longer, the presence of recurrent UTI and high levels of WBC, PNL, ESR and CRP significantly increased renal damage in the patients (p<0.001). It was determined that USG and VCUG have low sensitivity regarding prediction of renal damage.

Conclusion: Determination of renal damage rate by clinical and laboratory data detected at patient admission may contribute to a reduction in morbidity and mortality rates by applying an appropriate follow-up and treatment modality.

Key words: Urinary tract infection, child, risk factors, renal scar, fever.

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Öz

Amaç: İdrar yolu enfeksiyonu (İYE) çocukluk çağının önemli enfeksiyon hastalıklarından birisidir. Bazı çocuklarda renal skar gelişimine neden olarak uzun dönemde ciddi komplikasyonlara neden olmaktadır. Bu çalışmada akut piyelonefrit kliniği ile başvuran çocuk hastalarda renal hasar gelişimindeki risk faktörlerinin belirlenmesi amaçlanmıştır.

Gereç ve yöntem: Çalışmamızda Pamukkale Üniversitesi Tıp Fakültesi çocuk nefroloji polikliniğine başvuran idrar yolu enfeksiyonu tanısı ile takipli hastaların dosyaları retrospektif olarak değerlendirildi. Akut piyelonefrit tanısı idrar kültürü ve klinik bulgular ile kanıtlanmış ve Dimerkaptosuksinik asit renal sintigrafisi (DMSA) çekilmiş 197 hasta çalışmaya dahil edildi. Hastaların başvuru sırasında saptanan ve anamnezden elde edilen klinik (ateş, tekrarlayan İYE, işeme disfonksiyonu vb.), laboratuar (C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESH), beyaz küre sayısı (BK), polimorfonükleer lökosit sayısı (PNL), ortalama platalet hacmi (MPV), trombosit sayısı, serum üre ve kreatinin düzeyleri) ve görüntüleme (üriner sistem ultrasonografi (USG), voiding sistoüretrografi (VSUG) ve DMSA sintigrafisi) bulguları incelendi.

Bulgular: Kız hastaların sayısı (n:153) erkek hastaların sayısından (n:44) anlamlı olarak daha yüksek saptandı (p<0,001). Hastaların tedavi öncesi ateş düzeyinin 38ºC ve üzerinde olması, klinik bulguların iki gün ve daha fazla süredir devam ediyor olması, tekrarlayan İYE varlığı, BK, PNL, ESH ve CRP yüksekliğinin renal hasarlanmayı artırdığı tespit edildi (p<0,001). USG ve VSUG' nin renal hasarlanmayı gösterme açısından düşük sensitiviteye sahip olduğu görüldü.

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Sonuç: Hastaların başvuru sırasında tespit edilen klinik ve laboratuar verileri ile renal hasarlanma oranı belirlenmesi bu hastalarda uygun takip ve tedavi ile morbidite ve mortalite oranının azaltılmasını sağlayabilir.

Anahtar kelimeler: İdrar yolu enfeksiyonu, çocuk, risk faktörleri, renal skar, ateş.

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Introduction

Urinary tract infection (UTI) is one of the important infectious diseases of childhood age [1, 2]. Although, the frequency varies depending on age and gender, particularly upper urinary tract infections are known to cause serious renal damage and late-term serious morbidity [1-5]. Urinary tract infection is defined as the infections due to localization and growth of most common bacteria and rarely viruses and fungi in any site of the urinary tract system [1, 2]. The infection of renal parenchyma and collecting system is considered as acute pyelonephritis while cystitis and urethritis are the terms indicating the infections of lower urinary tract system [1].

It has been reported that renal damage develops in 10-64% of the pediatric patients with acute pyelonephritis [1]. The factors responsible for development of renal damage in UTI are not yet clear. The development of renal damage may cause hypertension in the late term as well as it may manifest a clinical course progressing to gestational complications and chronic kidney failure [1, 5].

At the present time, renal cortical scintigraphy is the best technique that reveals the renal damage due to acute pyelonephritis [6, 8]. It has been reported that renal damage encountered by scintigraphic techniques performed during or a while after acute pyelonephritis is closely related with clinical and laboratory evidence detected at the beginning of the disease. Low age, high levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the presence of vesicoureteral reflux (VUR), high fever, delayed treatment and the presence of recurrent pyelonephritis are the risk factors suggested for development of renal parenchymal damage [8-19].

In the present study, it was aimed to investigate the risk factors in development of renal scarring in the patients that applied with clinical evidence of acute pyelonephritis and to compare the sensitivity of dimercaptosuccinic acid (DMSA) renal scintigraphy marked with Tc99m to ultrasonography and voiding cystourethrography (VCUG) in determination of renal damage.

Materials and methods

Data of the patients that admitted to pediatric nephrology polyclinic of Pamukkale University and that were diagnosed with urinary tract infection were retrospectively evaluated based on polyclinic patient files. The medical files of totally 480 patients followed-up with diagnosis of UTI were evaluated. The patients in whom diagnosis of urinary tract infection was not confirmed by urine culture, DMSA scintigraphy was not performed and the patients with an additional anomaly (major urogenital system anomaly, anorectal malformation, neurological and obstructive urological anomaly) were excluded from the study.

The study was approved by “Ethics Committee of Pamukkale University” of the hospital before the start of the study.

High fever (≥38ºC) detected by anamnesis and during examination, vomiting, restlessness, malnutrition and abdominal distention in the young pediatric patients, abdominal pain, side pain and costovertebral angle tenderness in the older pediatric patients were considered as the clinical evidence of acute pyelonephritis. The recurrent UTI, constipation and voiding dysfunction were questioned.

The definition of infection was based on the presence of pyuria alone or accompanied by hematuria, nitrite positivity and growth of ≥100,000 colonies/ml from one bacterium in the urine culture samples obtained by attaching urine drainage bag and transurethral catheter techniques in the young pediatric patients and midstream urine samples in the older pediatric patients. In addition to these findings, CRP positivity by immunoturbidimetric method (>0.5 mg/L), ESR value greater than 20 mm/hour by Westergren method and white blood cell count >10,000 K/μL in complete blood count test (by

Cell-Dyn 3700 device) were evaluated as the evidence of acute pyelonephritis.

Anthropometric data, clinical evidence, fever duration, voiding dysfunction, constipation, recurrent UTI, laboratory evidence, CRP, ESR, white blood cell (WBC) count, polymorphonuclear leukocyte (PNL) count, mean platelet volume (MPV), platelet count, serum urea, serum creatinine, proteinuria, leukocytouria, the presence of nitrite, erythrocytouria, urine culture, the findings of urinary system USG, VCUG and DMSA of all the patients were recorded.

VUR grading was performed according to the recommendation of International Reflux Study Committee (37). In the study, the patients with Grade 1 and 2 VUR, Grade 3 VUR and those with Grade VUR 4 and 5 according to VCUG results were grouped as mild, moderate and severe patients, respectively.

Statistical analysis

Statistical analysis of the study data was performed using SPSS Version 10.0 (Statistical Package for Social Sciences) software package. Frequency table was used for the descriptive statistics while paired quantitative values were compared by t-test, ANOVA test was performed for comparison between triple quantitative values and qualitative data was compared by carrying out Chi-Square analysis.

Results

The study included 197 patients. Of those, 44 (22.3%) were male and 153 (77.7%) were female. The ages of the pediatric patients ranged between 1 month and 16 years (mean 4.7±4.05 years). Mean age of the male patients was lower than that of female patients (4.7±4 years vs 5.45±3.9 years, respectively) (p<0.001).

Urine cultures revealed growth of E. coli, Klebsiella pneumoniae, Enterobacter spp, Pseudomonas spp, Proteus mirabilis and other bacteria (Morganella morganii, Serratia spp, Citrobacter spp, Candida spp) with rates of 79.2%, 8.6%, 5.6%, 2.5%, 2% and 2%, respectively.

It was determined that DMSA scintigraphy was performed on average 47±13 days (7-100 days) after treatment of acute pyelonephritis. DMSA results were normal in 53.8% (n=106) of those patients whereas acute changes and renal scarring were encountered in 37.6% (n=74) and 8.6% (n=17) patients, respectively.

The evaluation of DMSA results in terms of age groups showed abnormal scintigraphic findings in 35%, 56.7% and 42% of 0-1, 1-5 and 5≤ age group patients, respectively. No statistically significant difference was found between the age groups regarding the frequency of abnormal scintigraphic findings (p=0.053) (Figure 1).

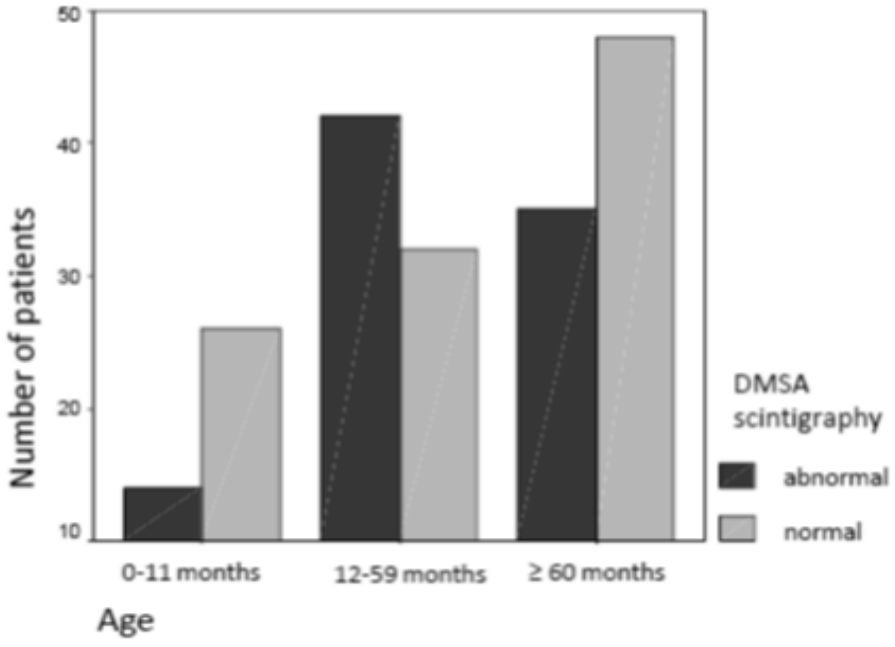

Figure 1. Distribution of DMSA scintigraphy findings by age groups
DMSA: Dimercaptosuccinic acid

It was found that body temperature of 38ºC and above detected during clinical course of acute pyelonephritis, persisting clinical evidence for 2 days or longer and the presence of recurrent UTI history significantly increased the probability of abnormal scintigraphic findings (p<0.001). DMSA scintigraphy results showed no significant correlation with voiding dysfunction and the presence of constipation (p>0.05) (Table 1). It was encountered that elevated white blood cell count, polymorphonuclear leukocyte count, CRP and ESR increased risk for development of renal damage (p<0.001) (Table 2).

Table 1. Relationship between clinical findings and scintigraphic changes

	DMSA scintigraphy Normal	DMSA scintigraphy Abnormal	Total	*p*
Fever				
<37 ^{0} (n, %)	65 (73.9)	23 (26.1)	88 (100)	
37^0-38^0 (n, %)	19 (48.7)	20 (51.3)	39 (100)	<0.001
> 38 ^{0} (n, %)	22 (31.4)	48 (68.6)	70 (100)	
Total (n, %)	106 (53.8)	91 (46.2)	197 (100)	
Duration of fever				
less than 2 days (n, %)	100 (63.7)	57 (36.3)	157 (100)	
2 days or longer (n, %)	6 (15)	34 (85)	40 (100)	<0.001
Total (n, %)	106 (53.8)	91 (46.2)	197 (100)	
Voiding dysfunction				
Yes (n, %)	27 (46.6)	31 (53.4)	58 (100)	
No (n, %)	40 (61.5)	25 (38.5)	65 (100)	>0.05
Total (n, %)	67 (54.5)	56 (45.5)	123 (100)	
Recurrent UTI				
Yes (n, %)	28 (32.6)	58 (67.4)	86 (100)	
No (n, %)	78 (70.3)	33 (29.7)	111 (100)	<0.001
Total (n, %)	106 (53.8)	91 (46.2)	197 (100)	
Constipation				
Yes (n, %)	16 (53.3)	14 (46.7)	30 (100)	
No (n, %)	90 (53.9)	77 (46.1)	167 (100)	>0.05
Total (n, %)	106 (53.8)	91 (46.2)	197 (100)	

DMSA; Dimercaptosuccinic acid

Table 2. Relationship between laboratory data and scintigraphic findings

	DMSA Normal	DMSA Abnormal	*p*
Urea (mg/dl)	20.6±7.5	22.4±8.3	>0.05
Creatinine (mg/dl)	0.40±0.11	0.44±0.15	=0.087
PNL (%)	55.7±9.4	62±10.1	<0.001
Platelet (K/µL)	335179.2±91070.4	341714.3±107141.9	>0.05
ESH (mm/saat)	20±16.4	50.9±20	<0.001
White Blood cell (K/µL)	11104.7±4547.1	13723.4±4952.9	<0.001
CRP (mg/L)	1.40±3.5	3.63±5.6	=0.001

PNL: polymorphonuclear leukocytes, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Only 19.3% of the patients had abnormal urinary system findings in USG. Also DMSA scintigraphy encountered pathology in 84.2% of the patients with abnormal USG findings whereas 15.8% of those patients had normal DMSA scintigraphy results. If scintigraphic evidence is accepted as gold standard according to these results; sensitivity, specificity, positive predictive value and negative predictive value of USG in predicting acute pyelonephritis findings were 35.2%, 94.3%, 84.2% and 62.9%, respectively 62.9% (Table 3).

Voiding cystourethrography was performed in 174 patients. No VUR was detected in 142 (72.1%) patients, Grade 1-2 VUR, Grade 3 VUR and Grade 4-5 VUR were identified in 16 (8.1%), 13 (6.6%) and 3 (1.5%) patients, respectively. DMSA scintigraphy also revealed pathology in 65.6% of the patients detected with VUR. If scintigraphic evidence is accepted as gold standard; sensitivity, specificity, positive predictive value and negative predictive value of VCUG in identifying pathology were found 25.6%, 88%, 65.6% and 57%, respectively (Table 3).

Table 3. Comparison of ultrasonography, voiding cystourethrography and DMSA scintigraphy findings

	Sensitivity (%)	Specificity (%)	Pozitive predictive value (%)
USG	35.2	94.3	84.2
VCUG	25.6	88	65.6

USG: Ultrasonography, VSUG: voiding cystourethrography

Discussion

It has been found in the present retrospective study that fever degree, fever duration, the presence of recurrent UTI, increased white blood cell count and elevated levels of ESR and CRP increased the risk of renal damage. DMSA scintigraphy results of the patients indicated that approximately half of the patients had renal damage and that renal damage predominantly involved acute changes.

There are studies in the literature that showed the relationship between development of renal scarring and fever degree in the patients who admitted with acute pyelonephritis. Pecile et al. [10] have found in their study on 316 pediatric patients that the detection rate of abnormal finding in DMSA scintigraphy was 17% in the patients with pretreatment maximum body temperature <38ºC whereas that rate was 74% in the patients with body temperature >39ºC. Similarly, it was also determined in our study that the presence of high fever degree increased the risk for renal damage and that this correlation was statistically significant. In addition, delayed fever duration or delayed treatment onset for pyelonephritis has been also reported as a risk factor for development of renal scarring [11]. Also we have determined that DMSA scintigraphy was affected by 85% in the pediatric patients with finding of high fever for 2 days or longer in our study. However, it has been suggested in the recent times that delayed treatment onset is not a risk factor for development of renal scarring and that once occurrence of parenchymal affection at the beginning of infection will result in renal damage [12]. This theory has been supported by two separate studies that evaluated 213 and 287 pediatric patients. It has been emphasized according to these two studies that preventing development of acute pyelonephritis is essentially more critical as well as treating acute pyelonephritis [12, 13, 20].

Yuksel et al. [9] have reported that the detection rate of abnormal scintigraphy finding was 62% when the time of performing scintigraphy was limited by the first 7 days after onset of pyelonephritis whereas the detection rate of abnormal scintigraphy finding decreased to 49% when the time of performing scintigraphy was limited by 30 days. We obtained similar results with this study. In pediatric patients with acute pyelonephritis, the detection rate of abnormal scintigraphy findings decreases as the time interval between the onset of the disease and the time of scintigraphy increases. This result supports the conclusion that risk for development of renal scarring can be reduced by treatment.

It is accepted that patient age is an important risk factor for development of renal scarring after acute pyelonephritis and that risk increases as

the patient age decreases. It has been reported that infants (below one year of age) carry the highest risk while the pediatric patients aged over 5 years carry lower risk [21, 22]. On the contrary, some studies have reported that age is positively correlated with the development of renal scarring [9, 10]. Yuksel et al. [9] have carried out a study on 201 patients with acute pyelonephritis aged between 0-14 years and identified abnormal scintigraphy findings with the rates of 22%, 47% and 53% in the pediatric patients aged below one-year-old, between 1-5 years and over 5 years, respectively. Also in our study, the rates of renal damage were 35%, 56.7% and 42% in the pediatric patients aged below one-year-old, between 1-5 years and over 5 years, respectively. Even though, the detection rate of abnormal scintigraphy finding was found higher than the other groups, however, no statistically significant difference was found between the age groups regarding detection rate of abnormal scintigraphic finding.

It has been demonstrated that irreversible renal damage occurs due to inflammation, interstitial injury and fibrosis that develop during acute pyelonephritis. This state is defined as the development of renal scarring displayed with renal scintigraphic examination. In addition, some authors have shown that inflammatory process continues even after recovery of urinary tract infection [23, 24]. Febrile recurrent UTI has been identified to be an independent risk factor for renal scarring in a prospective study conducted on 565 pediatric patients with febrile UTI and/or VUR. It has been observed in the same study that DMSA scintigraphy findings were normal during follow-up process in 76% of the patients despite recurrent febrile UTI episodes [25]. In also our study, normal scintigraphic findings were monitored in 32.6% of the patients with recurrent urinary tract infection. Although, no reason for nonoccurrence of renal scarring despite recurrent UTIs in some pediatric patients, it has been suggested that genetically protective factors may be present. It is considered that immune response of the host has a critical role in development of renal scarring [20]. DMSA is gold standard in the diagnosis of acute pyelonephritis. However, scintigraphy is most commonly not performed during diagnosis since it is an invasive procedure. The fact that some patients followed-up with diagnosis of pyelonephritis may not be a true case of pyelonephritis may also affect these results.

High white blood cell count and increased levels of CRP and ESR are the important laboratory parameters. Several studies have reported that there is a positive correlation between development of renal damage and high white blood cell account. Doganis et al. [12] have ascertained in their study on 278 patients that mean white blood cell count was significantly higher in the patients with abnormal scintigraphic findings. Similar results were obtained also in our study. However, there are also some studies that demonstrated that there is no relationship between white blood cell count and renal damage [26, 27]. In our study, mean CRP level was found significantly higher in the patients with abnormal scintigraphic findings compared to those with normal scintigraphic findings. CRP is one of the most important laboratory parameters in differentiation between upper and lower urinary tract infections. Therefore, many studies have addressed the relationship between CRP and renal damage. The studies have shown that the patients with abnormal findings in DMSA scintigraphy after acute pyelonephritis had significantly higher CRP levels. In contrast to other studies, Jakobsson et al. [8] have found no difference between CRP levels of the patients detected and not detected with renal scarring in DMSA scintigraphy. ESR is also one of the distinctive criteria like CRP in diagnosis of acute pyelonephritis. Garin et al. [16] have reported that ESR has higher sensitivity than CRP in diagnosis of acute pyelonephritis. The studies have shown that ESR values of the patients with renal damage than those without renal damage [9, 12, 16]. Similarly, with the studies in the literature, mean ESR values of the group with abnormal scintigraphy findings were found statistically higher than that of the group with normal scintigraphy findings in also our study.

Even though, ultrasonography does not provide adequate information about renal functions, it is still the primarily performed imaging method in diagnosis of the pediatric patients. There are studies in the literature that shows the efficacy of ultrasonography in detection of renal damage [5, 6, 28]. Christian et al. [28] have carried out a study on 990 patients and obtained

a low sensitivity rate of ultrasonography such as 21.7% in detection of renal cortical scarrings. Moorthy et al. [29] have determined a sensitivity rate of 47.2% and a specificity rate of 91.8% for ultrasonography regarding detection of diffuse renal scarring. Yuksel et al. [9] have carried out a study on 201 patients with urinary system infections and the sensitivity and specificity rates of ultrasonography in detection of renal cortical scarrings were found 29% and 90% in this study, respectively. Compared with the results of DMSA scintigraphy scan accepted as the gold standard; our results demonstrated that ultrasonography has low sensitivity although it has a high specificity in detection of renal scarring. Currently, we have concluded that ultrasonography cannot be replaced with DMSA scintigraphy.

The relationship between UTI, VUR and development of renal damage has been demonstrated in many studies. The prevalence of VUR has been reported to be approximately 30% in the pediatric patients who had febrile UTI for the first time. However, the frequency of VUR in the healthy population is not known [1]. The present study showed that VUR was detected in 18.4% of the patients that had pyelonephritis. That rate was reported to be 22% by Yuksel et al. [9]. In our study, sensitivity, specificity, positive predictive value and negative predictive value of VCUG in identifying pathology were found 25.6%, 88%, 65.6% and 57%, respectively. In the study of Moorthy et al. [4], senstivity and specificity rates of VCUG regarding detection of diffuse renal scarring to be 50% and 89.9%, respectively. Yuksel et al. [9] have reported the sensitivity and specificity rates of VUCG in detection of renal cortical scarrings to be 33% and 94%, respectively.

In conclusion, urinary tract infection is an important infectious disease that should be considered seriously and treated meticulously. The rate of renal damage can be determined by the clinical and laboratory data obtained at baseline admission of the patients. Taking late-term serious complications into consideration, morbidity and mortality rates can be reduced by appropriate management and treatment

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Authors' contributions

S.Y. built the main idea and hypothesis. B.S. arranged the material and method section and evaluated the data. The article was written, reviewed and necessary corrections were made by T.B. and S.Y. In addition, all authors discussed the entire study and approved the final version.