RADIOLOGIC EVALUATION OF CHILDREN WITH UPPER URINARY TRACT INFECTION

ÜST ÜRİNER SİSTEM ENFEKSİYONLU ÇOCUKLARIN RADYOLOJİK DEĞERLENDİRİLMESİ

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Özet

Bu çalışmanın amacı üst üriner sistem enfeksiyonlarını değerlendirmede radyolojik yaklaşımı belirlemek ve erken renal kortikal defekt gelişiminde etkili olan risk faktörlerini tespit etmektir. Kortikal sintigrafi, ultrasonografi (US), ve intravenöz pyelografi (İVP) ile sırasıyla çocukların %48.5'i, %34.7'si ve %14.3'ünde renal değişiklik saptandı ($p<0.001$). Renal parankimal inflamasyon tanısı için sintigrafiye göre US'nin sensitivitesi %67.3, İVP'ninki ise %23.6 idi. Beş yaşından büyük çocuklarda renal skar insidansı daha düşüktü ($p<0.05$). Renal lezyonları belirlemede ateş ve inflamatuvar reaktanların (C-reaktif protein, eritrosit sedimentasyon hızı, kan lökosit sayısı) sensitivitesi sırasıyla %58.1, %48.2, %22.1 ve %22.7 idi. Renal skar gelişiminde cinsiyetin ve enfeksiyon etkeninin etkisi saptanmadı. 103 hastanın %12.2'sinde vezikoüreteral reflü (VUR) bulundu. VUR ile kortikal defekt arasında anlamlı ilişki tespit edildi ($p<0.05$). Renal skarı saptamada sintigrafinin US ve İVP'den daha sentitif bir yöntem olduğu ve pyelonefrit düşünülen vakalarda ilk basamak görüntüleme yöntemi olarak kullanılmasının uygun olacağı kanısına varıldı.

Anahtar kelimeler: *İdrar yolu enfeksiyonu, Radyolojik değerlendirme, Renal parankimal skar, Risk faktörü, Çocuk*

Summary

The purpose of this prospective study was to investigate the most relevant radiological approach for the evaluation and to determine risk factors in the development of early renal cortical defects in 103 patients with upper urinary tract infection. Cortical scintigraphy, ultrasonography (US) and intravenous pyelography (IVU) showed renal changes in 48.5%, 34.7% and 14.3% of children, respectively ($p<0.001$). For the diagnosis of renal parenchymal inflammation, the sensitivity of US according to the scintigraphy was 67.3% and the sensitivity of IVU according to the scintigraphy was 23.6%. Children more than 5 year of age had lower incidence of renal lesions than did younger children ($p<0.05$). The presence of fever and inflammatory signs (C-reactive protein, erythrocyte sedimentation rate, white blood cell count) had a 58.1%, 48.2%, 22.1% and 22.7% sensitivity in identifying renal lesions. No association with sex or infective organism was established. Among 103 patients vesicoureteric reflux was present in 12.2%. An association between a cortical defect and the presence of VUR was determined ($p<0.05$). We found that cortical scintigraphy is more sensitive than US and IVU in detecting renal changes, and we believe that it should be added to the initial examination of children with suspected pyelonephritis.

Key words: *Urinary tract infection, Radiologic evaluation, Renal parenchymal scar, Risk factor, Children*

Introduction

Concern with childhood urinary tract infections (UTIs) focuses not so much on the morbidity of the acute infection but on the risk of delayed clinical outcomes resulting from renal parenchymal damage. One author has suggested a risk of 1:100 for hypertension and 1:500 for renal failure for children with a history of UTIs, though the basis for this estimate was not clearly described (1). It was reported that the incidence of urinary tract pathology for girls and boys with UTI were 28% and 47%, respectively (2). The risk of renal scarring is known to be higher in children with urinary tract pathology as compared to those with normal anatomy. This risk is particularly high in patients under the age of five. It was also reported that one third of these scars develop during the first UTI episode (3). Many investigators suggest radiological assessment after the first UTI episode (2,3). Advocates of routine diagnostic imaging for all children with their first UTI maintain that early detection of urologic anomalies will lead to improved outcomes. The use of long-term antimicrobial prophylaxis and, in some cases, urologic surgery is believed to reduce progressive scarring caused by recurrent infection and obstruction, with the ultimate goal of preventing hypertension and renal insufficiency. The aim of our study was to determine the most relevant radiological imaging method for assessment of patients with UTI and to identify factors that might be used to predict the development of renal scars in children with UTI.

Patients

Of patients having positive bacterial colonization in their urine samples 103 patients with upper UTI were included in this prospective study. Proved infection included all pure growths of more than 10^5 CFU/mL of a single urinary pathogen from midstream urine, all pure growths of more than $50x10^3$ CFU/mL of a single urinary pathogen from a catheter specimen or any pure growth from a suprapubic bladder aspirate (4). From each patient a detailed medical history was taken and systemic physical examination was performed. Investigations included white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). The cases were evaluated by modified Jodal Criterias (5) and diagnosed as upper UTI. The patients underwent ^{99m}Tc-DMSA scintigraphy, intravenous urography (IVU), ultrasonography (US) within 7 days after beginning antibiotic treatment. ^{99m}Tc-DMSA scintigraphy was taken as the gold standard method in determining renal parenchymal infection. Renal cortical scintigraphy was done in all patients. For ^{99m}Tc-DMSA scanning a GE 400 ACT Starcam camera with a computer system was used. Two to three hours after the intravenous injection of 2 Mbq/kg ^{99m}Tc-DMSA, anterior, posterior, right lateral and left lateral images were obtained. Focal areas in the renal parenchyma showing diminished radioactivity were referred to as "defects". The localized or generalized uptake defects was accepted as an indicator of acute infection. The ultrasound examinations in all patients were performed by consultant radiologist using a 3.5 Mhz probe on ultrasound machine (Toshiba SAL 77A). The kidneys was assessed for presence of congenital anomalies, renal scarring and for changes related to acute infection (swelling of the kidney, generalized or localized increased or decreased echogenity, loss of the cortico-medullary differentiation). Of 103 patients, 91 cases had undergone IVU by using the conventional Toshiba KXO-50 F X-ray device. During IVU, sodium megluminedieatrizoat (Urografin®) was used as contrast material. Anatomical pathologies related to the urinary system were investigated, just like renal parenchymal loss and calyxeal deformities which were evaluated as renal scarring. There were IVU findings related to acute infection. After the infection had been eradicated and at least 8 weeks of infection-free period had been achieved, 74 patients underwent voiding cystourethrograms (VCUG). VCUG was performed according to standard technique using a cystographic contrast agent instilled by catheter under gravity. Vesicoureteric reflux was diagnosed and graded according to the international classification (6). The images were independently assessed by a same radiologist or nuclear medicine physician (renal cortical scan) without knowledge of the other imaging results. Statistical analysis were measured by the X^2-test, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A p value less than .05 was considered significant.

Table 1. *According to the ^{99m}Tc-DMSA Scintigraphy the Sensitivity, Specificity, Positive Predictive Value(PPV), Negative Predictive Value (NPV) of Radiologic Imaging Methods, and Presence of Fever and Inflammatory Signs*

	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)
fever	58.1	100.0	100.0	25.0
CRP	48.2	100.0	100.0	48.2
WBC	22.7	100.0	100.0	16.8
ESR	22.1	100.0	100.0	20.8
US	67.3	100.0	100.0	72.8
IVU	23.6	100.0	100.0	53.3

CRP: *C-reactive protein*, WBC: *White blood cell count*, ESR: *Erythrocyte sedimentation rate*, IVU: *Intravenous urography*, US: *Ultrasonography*

Results

103 children, 72 (69.9%) girls and 31 (31.1%) aged 0.5 month to 15 years (mean 5.9 years) entered the study. 29 of 54 patients (53.7%) with a body temperature above 38.5 °C had an abnormal DMSA scintigraphy compared to 21 of 49 (42.9%) with a body temperature less than 38.5 °C. CRP level over 20 mg/L was noted in 71 (68.9%), WBC over normal range for age was noted in 44 (42.7%) and ESR over 20 mm/hour was noted in 42 (40.8%) of 103 patients. In 64 patients (62.1%) ultrasonographic findings were found to be normal. 37 patients (34.7%) had renal scarring. Two patients (1.9%) had congenital anomalies (one renal agenesis, one hydronephrosis), one patients (1.0%) had urolithiasis. Of 103 patients, 91 cases had undergone IVU. In 76 patients (83.5%) urographic findings revealed normal urinary system. Four patients (4.4%) had congenital anomalies (one ureteropelvic junction obstruction, one double collecting system, one renal agenesis, one hydronephrosis), two patients (2.2%) had urolithiasis, and 13 patients (14.3%) had renal cortical scarring. IVU is much more sensitive in detecting congenital anomalies and urolithiasis than US. In 53 patients ^{99m}Tc-DMSA scans revealed normal kidneys. Fifty patients (48.5%) were found to have parenchymal defects, seven of which were bilateral and multiple. Topographic analysis of lesions showed that 49 % were localized to the upper poles, 14% to the middle third, and 24% to the lower poles of the kidneys. Scarring was significantly more frequent in the upper polar areas ($p<0.001$). Cortical scintigraphy, ultrasonography (US) and intravenous pyelography (IVU) showed renal changes in 48.5%, 34.7% and 14.3% of children, respectively ($X^2=26.4$, $p<0.001$). According to the ^{99m}Tc-DMSA scintigraphy the sensitivity, specificity, PPV, NPV of radiologic imaging methods (US, IVU), and presence of fever and inflammatory signs (WBC, CRP, ESR) were given Table 1 in the upper urinary tract infection. The sensitivity of US was calculated to be 67.3%, NPV 72.8%, while the sensitivity of IVU was found to be 23.6% and NPV 53.3%. DMSA scintigraphy is much more sensitive in detecting cortical defects than either renal sonography or intravenous urographs. Presence of fever had 58.1% sensitivity and 25.0% NPV, CRP had 48.2% sensitivity and 48.2% NPV, WBC had 22.7% sensitivity and 16.8% NPV, and ESR had 22.1% sensitivity and 20.8 NPV in identifying renal lesions. Among these properties presence of fever and CRP level over 20 mg/L were risk factors for renal scarring. Seventy-four patients underwent VCUG. Nine patients (12.2%) has vesicoureteric reflux (VUR).

Table 2. *Distribution of Cortical Defects by the Presence and Absence of Vesicoureteric Reflux*

reflux	defect		no defect		total	
	n	%	n	%	n	%
present	7	77.8	2	22.2	9	12.2
absent	31	47.7	34	52.3	65	87.8
total	38	51.4	36	48.6	74	100.0

Note: *VCUG can not be done in 12 patients with cortical defect*

Table 3. *Distribution of Cortical Defect and Vesicoureteric Reflux by Age*

age (year)	defect		no defect		reflux		no reflux		total	
	n	%	n	%	n	%	n	%	n	%
0-2	8	57.1	6	42.9	5	35.7	9	64.3	14	13.6
2-5	26	57.8	19	42.2	1	2.2	44	97.8	45	43.7
6-10	12	37.5	20	62.5	2	6.3	30	93.7	32	31.1
>10	4	33.3	8	66.7	1	8.3	11	91.7	12	11.6
total	50	48.5	53	51.5	9	8.7	94	91.3	103	100.0

Five children had grade 1 reflux (two bilateral), two children had grade 2 reflux and two children had grade 4 reflux (one bilateral). No children had grade 5 reflux. The results comparing VUR and cortical defects are seen in Table 2. These results show an association between a cortical defect and the presence of VUR (X^2=3.89, p<0.05). Of 38 patients with cortical defect, VUR was not shown on VCUG in 31. Conversely, of nine patients with VUR, two had no cortical defect. Of five patients with grade 1 reflux, three had cortical defect. In these cases ultrasonographic and urographic findings were normal. In two patients with grade 2 reflux US and ^{99m}Tc-DMSA scans revealed parenchymal defect, but urographic finding were found to be normal. In two patients with grade 4 reflux three radiographic evaluation revealed cortical defect. No association between the grade of VUR and the presence of cortical defects was found (X^2=1.16, p>0.05), with more defects occurring as the severity of VUR increases. Also, no association was found between the patient's sex and either cortical defects and VUR (p>0.05). The most common infective organism, Escherichia coli, was present in 68 (66,0 %) patients; the remaining patients were infected by Enterobacter, Proteus, Klebsiella or others. No association was found between the type of infective organism and cortical defects. Table 3 shows the distribution of cortical defects and VUR by age. The frequency of a cortical defect decreases with age, and the most marked reduction occurs after 5 years of age. Defects were present in 34 (57.6%) of 59 patients up to 5 years old and in only 16 (36.4%) of 44 patients more than 5 years old (X^2=4.56, p<0.05). Table 3 shows that prevalence of VUR decreases after 2 years of age. VUR was present in five (35.7%) of 14 children 0-2 years old and in only four (4.5%) of 89 children more than 2 years old. Thirty (29.1%) of the patients had a history of recurrent UTI, others had their first diagnosed UTI. Of the 73 (70.9%) children who had their first episode of UTI, 31 (42.5%) had renal parenchymal changes. Among the 30 children with a history of multiple UTIs, renal changes were found in 19 (63.3%). However, this difference did not reach statistical significance (p>0.05).

Discusssion

Pyelonephritis is usually diagnosed on the basis of clinical signs and positive urine culture result. No clinic, laboratory or radiologic examination is available as a "gold standard" for diagnosis. For deciding a treatment scheme and for an appropriate follow-up, localization of the infection is of utmost importance. Patients with acute pyelonephritis are logical candidates for scarring (4). Therefore, it is important to detect an early defect seen because the defect represents either an established scar or acute pyelonephritis with potential for scarring. Defects of acute pyelonephritis will resolve, unless they subsequently become scars. Up to 80% of defects have been found to persist, as shown at follow-up after 6 months (7). Renal parenchymal radioisotope scanning has considerably high sensitivity and selectivity for the imaging of both renal parenchymal infection. In an animal experimental study it was suggested that DMSA scanning performed within the first five days from the onset of the disease was beneficial for the differential diagnosis of upper and lower urinary tract infection. In the same study repeat DMSA scans of appropriately treated cases taken on the 28th day of infection showed complete recovery, while in the untreated cases the initial defects persisted in repeat 28th day DMSA scans (8). In our study 103 patients with acute pyelonephritis underwent DMSA scanning, US and IVU within 7 days after beginning antibiotic treatment. These three imaging methods were compared with respect to their superiority in determining renal parenchymal pathology. The sensitivity of US and IVU as compared to DMSA scan were 67.3% and 23.6%, respectively.

Bircan et al (9) found that the sensitivity of US and IVU as compared to DMSA scan were 25% and 9.09%, respectively. In the study by Traisman et al (10) the sensitivity of IVU and US for determining upper UTI was reported to be 24% and 42%, respectively. Among the radiographic modalities the less beneficial imaging method was determined to be IVU. Evaluation includes imaging to show reflux (VCUG), scarring (nuclear scan or US), and structural abnormalities (IVU or US). Also, in selecting a radiological approach the ionizing radiation directed towards kidney, bladder and gonads should always be taken into account. Because gonads are exposed to higher radiation by IVU than by ^{99m}Tc-DMSA scanning (3), the use of this method as the first step in diagnosis is definitely unjustifiable. Cortical scintigraphy ^{99m}Tc-DMSA is much more sensitive in detecting cortical defects than either renal sonography or intravenous urography (9). In the present study, all 103 patients had bacteriuria verified by urine culture together with clinical symptoms. However, only 48.5% of the patients had abnormal findings at DMSA scintigraphy performed in association with the acute infection. In the study reported by Bircan et al (9), children underwent DMSA scanning, IVU and US before the onset of treatment; the incidence of abnormal DMSA scintigraphy was found 71.4%. In the other study, DMSA scintigraphy was performed at a median of 10 days after the start of treatment and was abnormal in 42%. The timing of the DMSA scintigraphy, as related to the start of antibiotic treatment, seems to be of great importance for the outcome of the scintigraphy. If DMSA scintigraphy is used in acute UTI to demonstrate renal involvement, it should thus be performed as soon as possible, i.e. within days, after clinical suspicion of pyelonephritis has been raised. The clinical diagnosis of acute pyelonephritis is traditionally based on urine culture, flank pain, fever, elevated CRP level and other laboratory tests. Using DMSA scintigraphy as the "gold standard" for renal involvement in the present study, presence of fever and CRP level over 20mg/L as an indicator of renal involvement demonstrated a high sensitivity (58.1%, 48.2%, respectively) and a high negative predictive value (25.0%, 48.2%, respectively). Stokland et al (11) found that the sensitivity (95%) and NPV (88%) of CRP were high. Also in the same study CRP level and body temperature correlated significantly with abnormalities at DMSA scintigraphy in univariate statistical analyses (11). Thus, these signs are useful as predictors of renal involvement but they are unreliable. In our study, acute renal lesions were higher in the upper poles than middle third and lower poles of the kidneys, whether there was a reflux or not. Scarring was significantly more frequent in the upper polar areas ($p<0.001$). Hannerz et al (12) found that frequency of lateral scars was significantly lower than in the upper and lower poles ($p<0.05$). Benador et al (13) found that scars were evently distributed between poles of the kidneys. However, our data confirmed the high percentage of polar lesions previously found (12). US is generally known to have low sensitivity in demonstrating renal parenchymal changes according to DMSA scanning (2,10). Similarly our findings IVU has not been suggested as a routine procedure except for explaining obstructive findings in cases with urinary stones and for determining congenital urinary anomalies according to US in recent years (14,15). This study demonstrate an association between early cortical defects and age and VUR. No association was established between cortical defects and sex or infective organism. In other studies, age has also been established as an important factor in the pathogenesis of renal scars, with new scars rarely occurring in children more than 5 years old (16,17). But Stokland et al (11) found that there was an increased frequency of abnormal DMSA scintigraphy with increasing age ($p<0.01$). VUR is a known risk factor for renal scarring. Similar findings were made by other reports (16,18). DMSA scintigraphy abnormalities decreased with increasing age in our study. This may have been secondary to the higher incidence of reflux in the younger age groups. The question whether the detection of reflux in children with normal DMSA scintigraphy is necessary for identification of those who are at risk of future renal scarring. In conclusion, regardless of the sex of the patients, all children with UTI require investigation, ideally after the first UTI, by at least two imaging techniques. DMSA scan are the procedures of choice for all patients with UTI, whether the patient is a boy or a girl and whether the infection is the initial episode or a subsequent one. In centers, where DMSA scan is not available we suggested US performed to be first imaging method. When treatment of infection is completed VUR should investigated by VCUG in all cases. We suggest DMSA scan, where available, as the method choice. It should be performed as soon as possible. IVU was suggested as a routine procedure in cases with urolithiasis and for determining congenital urinary anomalies. Pediatricians should have an increased awareness of the benefits of renal cortical scintigraphy in the patient with acute pyelonephritis.

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