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Results of a five-year study of ^{99m}Tc-DMSA renal scintigraphy in children and adolescents following acute pyelonephritis

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Abstract

BACKGROUND: Renal scintigraphy, generally using ^{99m}Tc-DMSA, is the accepted reference standard for detection of renal cortical changes. The timing of the test, i.e., whether an acute ^{99m}Tc-DMSA scan, a follow-up only or both scans should be performed, however, remains open to discussion. In our study, a six-month follow-up DMSA scan was performed in all the children diagnosed with a first attack of acute pyelonephritis (APN) in two large paediatric clinics of Charles University's 3rd School of Medicine in Prague during a five-year period. All diagnoses were confirmed by a paediatric nephrologist.

MATERIAL AND METHODS: 382 children (267 girls, 115 boys) aged between 7 months and 19 years were included in the study. For analytical purposes, the patients were divided into 4 age groups: I — less than 1 year of age, II — 1–5 years, III — 5–10 years, and IV — 10–19 years. In all children younger than five years, a micturition cystourethrogram (MCUG) for detection of vesicoureteric reflux (VUR) was performed between one and three months after the APN episode. Static renal scintigraphy, using an HR collimator with parallel holes was performed using a planar Gamma camera MB 9200 (Gamma Budapest) in all children six months after APN, with a complement of pinhole images, SPECT or PSPECT of the kidneys.

RESULTS: 1. In group I, all four children with positive VUR on MCUG had a pathological DMSA scan, while only two of the 32 patients with negative VUR had a pathological DMSA. 2. In group II, 17 children had VUR on MCUG, six of them with a pathological and 11 with a normal DMSA scan. Most of the 221 children without VUR had a normal DMSA scintigraphy; pathological findings were present in 17 children only. 3. In group III, all children with VUR, but only 5 out of 53 without VUR, had a pathological DMSA scan. 4. Five out of 50 children in group IV had a pathological DMSA.

CONCLUSIONS: APN occurred most frequently in group II (62.3%, or 238 children) and ranged between 10–15% in the remaining groups. APN was found very frequently in boys less than one year old and showed a marked decrease with increasing age. Among girls, however, APN incidence was observed to increase with age. Pathological renal changes were present in children with, as well as without, VUR. The incidence of pathological DMSA findings six months after APN was relatively low (44/382 patients, or 11.5%). Regular monitoring of these children is very important for detection of renal scarring.

Key words: renal scintigraphy, ^{99m}Tc-DMSA scan, acute pyelonephritis, vesicoureteric reflux, childhood

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Introduction

Urinary tract infection (UTI) is one of the most common diseases in childhood. UTI may be limited to the bladder, i.e., cystitis, or may involve renal parenchyma, i.e., acute pyelonephritis (APN), defined as fever over 38.5æC, high level of C-reactive protein or erythrocyte sedimentation rate, leucocyturia and positive urinary culture [1]. The clinical presentation of APN may be non-specific and varies according to factors such as the patient's age and level of infection (i.e., whether the infection involves kidneys or lower urinary tract only).

Renal scintigraphy, generally using ^{99m}Tc-DMSA, is the accepted reference standard for detection of renal cortical changes [2]. It may be used during an attack to localize UTI and thus determine the risk of scarring from the current infection, and/or in a sequential follow-up to monitor the development and progression of scarring [3, 4]. The Scientific Committee of Radionuclides in Nephrourology attempted to reach a consensus on modalities of application of renal scintigraphy in children with UTI [5]. The strategic approaches to the handling of patients with UTI vary and may reflect the health-care delivery system in a particular area. Moreover, the paediatric nephrologist´s judgment differs frequently from that of the nuclear medicine physician and considerable discrepancies exist even among the opinions of nuclear-medicine specialists. The question of timing of the ^{99m}Tc-DMSA scan, i.e., whether to perform an acute scan, a follow-up scan only or both, remains open to discussion. Some authors consider acute renal scintigraphy unnecessary because half of the acute lesions are transitory and disappear with time [6, 7]. Furthermore, many paediatric nephrologists base the diagnosis of complicated UTI on clinical and biological findings alone and deem scintigraphy to be diagnostically unnecessary [8, 9]. However, patients lacking clinical and biological signs or whose urine cultures are negative or equivocal may still have UTI and obvious acute renal lesions [10, 11], while patients with a full clinical picture of complicated UTI may or may not show abnormalities on a renal scintigraphy [1, 10–12].

Many diagnostic tests of UTI use radiation. In an effort to examine the affected children with minimal radiation exposure and following the paediatric nephrologist´s recommendation and guidelines on ^{99m}Tc-DMSA scintigraphy in children [13], we performed a DMSA scan six months after the first attack of APN in a large group of paediatric patients in the period between 2000 and 2004. The purpose of the study was to determine the appropriate medical care in children with APN and the frequency of pathological scintigraphic changes persisting among the patients six months after the first APN attack.

Material and methods

The patient sample includes all the children diagnosed with the first episode of APN in two large, University-affiliated paediatric clinics (Kralovske Vinohrady and Bulovka) in Prague during 2000-2004. Each diagnosis was confirmed by a paediatric nephrologist, based on clinical and laboratory examinations. Altogether, 382 children (267 girls, 115 boys) aged 7 months to 19 years were examined six months after APN. For analytical purposes, the patients were divided into 4 age groups:

— group I — less than 1 year;
— group II — 1–5 years;
— group III — 5–10 years;
— group IV — 10–19 years.

Table 1. Distribution of patients with APN by sex and age

Age (years)	Total	Boys	Girls
0–1	36 (9.4%)	28 (77%)	8 (23%)
1–5	238 (62.3%)	77 (32%)	161 (68%)
5–10	58 (15.2%)	7 (13%)	51 (87%)
10–19	50 (13.1%)	3 (6%)	47 (94%)
Total	382 (100.0%)	115 (30%)	267 (70%)

APN — acute pyelonephritis

The patient distribution by sex and age is summarized in Table 1.

In all children younger than five years of age, a micturition cystourethrogram (MCUG) for detection of vesicoureteric reflux (VUR) was performed between one and three months after the APN episode. Static renal scintigraphy, using an HR collimator with parallel holes, was performed in all 382 patients 6 months after the APN episode on a planar Gamma camera MB 9200 (Gamma Budapest), with the patient in a supine position, in 4 projections. The renal images were performed two hours after radiopharmaceutical administration. The activity for injection was calculated using a body surface area scaling factor on the adult dose activity of 100 MBq ^{99m}Tc-DMSA. A 0.3 mg/kg dose of intranasal midazolam was given for sedation as needed to restless or anxious children. Data of computer-assisted collection were 200,000 counts/image, matrix 128 × 128, zoom 3–4. The report of static scintigraphy includes a mathematical analysis of global and separate renal functions.

Images using a pinhole collimator or PSPECT (pinhole single photon emission computer tomography) of the kidneys were completed in small children with equivocal or pathological findings on static scintigraphy. Pinhole images of each kidney (2 mm hole size) were performed on a planar Gamma camera in supine and lateral positions. Data of computer-assisted collection were 300 s/image, matrix 128 × 128, zoom 1. PSPECT of one or both kidneys were performed on a single-detector tomographic camera APEX SPX with pinhole collimator (4 mm hole size) with 180° angle in clockwise direction, ZOOM 1–2, matrix 128 × 128 in children under 4 years of age. A Manglos algorithm was used for PSPECT reconstruction. In older children, SPECT (single photon emission computer tomography) of the kidneys was carried out using a two-detector camera HELIX or a single-detector tomographic camera APEX SPX (Elscint). Acquisition data were: 60 images/30–50 s, ZOOM 1–2, over a 180° or 360° angle, matrix 64 × 64. A Hanning filter was used for SPECT reconstruction before a review in the transverse, coronal, and sagittal planes.

Results

The results of DMSA scintigraphy and the relationship between VUR and the DMSA scans are summarized in Tables 2 and 3:

— in group I, consisting of 36 children, 4 patients with positive VUR on MCUG had a pathological DMSA scan. Among the rest with negative VUR, a pathological DMSA scan was

Table 2. Results of a ^{99m}Tc-DMSA scan in patients six months after an APN episode by sex, age and presence of VUR

Patients		Positive VUR		Negative VUR		Total
Age [years]	Sex	Pathological DMSA	Normal DMSA	Pathological DMSA	Normal DMSA	
0–1 (group I)	Girls	2	0	0	6	8
	Boys	2	0	2	24	28
	Total	4	0	2	30	36
	Total	**4**		**32**		**36**
1–5 (group II)	Girls	4	6	12	139	161
	Boys	2	5	5	65	77
	Total	6	11	17	204	238
	Total	**17**		**221**		**238**
5–10 (group III)	Girls	3	0	4	44	51
	Boys	2	0	1	4	7
	Total	5	0	5	48	58
	Total	**5**		**53**		**58**
10–19 (group IV)	Girls	0	0	3	44	47
	Boys	0	0	2	1	3
	Total	0	0	5	45	50
	Total	**0**		**50**		**50**

APN — acute pyelonephritis; VUR — vesicoureteric reflux

Table 3. Relationship between VUR and pathological DMSA scan six months after an APN episode by age

Age [years]	Positive VUR	Pathological DMSA	Negative VUR	Pathological DMSA
0–1	4 (11.1%)	100.0%	32 (88.9%)	6.2%
1–5	17 (7.1%)	35.3%	221 (92.9%)	7.7%
5–10	5 (8.6%)	100.0%	53 (91.4%)	9.4%
10–19	0 (0.0%)	0.0%	50 (100.0%)	10.0%
Total	26 (6.8%)	57.7%	356 (93.2%)	8.2%

APN — acute pyelonephritis; VUR — vesicoureteric reflux

present in two cases only;
- of the 238 children in group II, 17 had VUR on MCUG. Only six of them had a pathological DMSA scintigraphy, while the remaining 11 children had normal DMSA. Most of the 221 children without VUR had normal DMSA scintigraphy; pathological findings were present in 17 patients only;
- among the 58 children in Group III, all those with VUR had a pathological DMSA scan but only five of 53 patients without VUR had a pathological DMSA scan;
- five out of 50 children in Group IV had pathological findings on the DMSA scan;
- APN occurred most often among children 1–5 years old (62.3 % of all patients) and ranged between approximately 10 and 15% in the remaining three age groups;
- among boys, the frequency of APN was highest in the youngest age group and decreased thereafter. In girls, on the contrary, APN increased markedly with age. The total numbers of patients with APN of both sexes decreased significantly among older children;
- positive VUR was detected in 6.8% of patients, the majority of whom (57.7%) had pathological DMSA changes (100%, 35% and 100%, respectively, in groups I, II and III);
- among the majority of the patients without VUR (93.2%), pathological DMSA scans were found in only 8.2% of all cases;
- altogether, pathological DMSA findings were present in 44/ /382 patients (11.5%) six months after an APN episode.

Discussion

A major clinical problem in children with UTI is the difficulty of identifying those at risk of having renal damage. Sequelae of renal scarring may include growth failure, hypertension, and, eventually, chronic renal failure [14]. Renal scars are present in 6–10% of children with UTI [15]. Patients with APN are logical candidates for scarring as an acquired renal scar can result from necrosis and fibrosis associated with acute inflammation. Defects of APN are resolved, unless they subsequently become scars. Ditchfield et al [16] found 80% of defects to persist at a follow-up after six months. The initial infection determines the subsequent degree of damage. Various factors exercise an influence on the genesis of renal damage in children.

Specific clinical signs, such as high fever, may signal a need for diagnostic imaging and are being used by nephrologists for this purpose. Stokland et al [7] demonstrated a positive correlation between renal damage and CRP, body temperature and

reflux. Children with high levels of CRP, high fever and dilating reflux had a risk of renal damage up to ten times higher than children with normal or slightly elevated CRP levels, no or mild fever, and no reflux. Jakobsson et al [1] found no difference between groups with or without scars with respect to the duration of fever and the levels of CRP or cell counts at the time of APN. Toxic metabolites released from infiltrating polymorphonuclear leukocytes have been shown to damage the renal tissue, while leucocyte-inhibiting drugs protect against acquired renal scarring.

Young age at first infection may be an important risk factor, with a higher prevalence of VUR and renal scarring being observed in small children. Boys are more susceptible before the age of one year; thereafter the incidence is substantially higher in girls [15, 17]. Our results confirm these trends, with a general decrease in incidence of APN in children after five years of age. Apart from the young age (less than five years), the risk factors for the development of renal parenchyma scarring include the time elapsed before the onset of the symptoms and initiation of therapy and the route of antibiotics administration. Levschenko et al. [18] compared the efficacy of 7-day (group A) and 3-day (group B) administrations of intravenous antibiotics, both followed by oral treatment in children with APN. DMSA scintigraphy was performed within the first days after admission and repeated 6 months later. In group B, the percentage of children with sequelae was significantly higher when the delay was more than one week. Other variables that may be associated with renal scarring are bacterial virulence, problems related to host resistance, and anatomic or functional abnormalities [14].

Renal scintigraphy using ^{99m}Tc-DMSA is being advocated as the preferred method for assessment of renal sequelae after APN [19]. Majd et al [20] evaluated the advantages and disadvantages of imaging modalities for clinical use and confirmed the value of DMSA even at present, in the era of improving technical capabilities of ultrasound, CT and MRI methodology. Ultrasound has a low sensitivity for APN. Spiral CT and MRI imaging appear to be equally sensitive but are not recommended for routine use. The disadvantages of MRI are high costs, the need for sedation and limited availability in an average clinical setting. Spiral CT is associated with high radiation dose and requires rapid intravenous injection of a large volume of contrast tracer.

Camacho et al [21] probed the prognostic value of DMSA scintigraphy performed during acute APN for outcome assessment. Their results demonstrated that children with abnormal DMSA had a higher frequency of VUR than children with normal DMSA. They concluded that children with normal DMSA during acute APN have a low risk of renal damage. Moorthy et al [22], in their retrospective data collection of 108 children aged under 1 year, reported VUR in 11.6% and scarring on DMSA in 3.7% of patients. Only 16% of kidneys with VUR had associated scarring, while 50% of scarred kidneys were not associated with VUR. The presence of VUR does not identify a susceptible population with an abnormal kidney on DMSA. Zaki et al [23] showed persistent parenchymal defects in 38% patients, but their study group included 32% children with VUR. Ditchfield et al [16] reported that 54 of the 88 patients (61%) with a cortical defect at scintigraphy did not have VUR demonstrated at MCUG. Conversely, 24% children had VUR and 53% of these had no cortical defect. They concluded that VUR and renal cortical scintigraphic defects frequently occur independently of each other. There is evidence that parenchymal changes occur predominantly in patients with grades IV and V VUR [1, 15, 17, 24], which has an impact on the size of renal lesions after an episode of APN. However, significant lesions may develop also in the absence of VUR [24].

Our results support these findings. Among our patients, VUR was detected in only 26/382 children (7%). More than half of them (15/26, or 57% patients) had pathological DMSA changes. Most of our children (356/382, or 93%) were without VUR and pathological DMSA scans were found in about 10% of all patients. The problems of VUR are usually resolved in older children. Our patients without evidence of VUR had pathological DMSA scans in 29/356 cases (8%) only.

Pathological DMSA changes were found in 44/382 patients (11%) as potential renal scarring. Very similar findings were found in the literature [15, 25, 26]. Hoberman et al [25] noted renal scarring in 9.5% children (26 of 275) after a repeated ^{99m}Tc DMSA scan. A systematic review of diagnostic imaging in childhood UTIs [27] yielded four studies of radiological follow-up more than six months after initial visit. Between 5 and 15% of the children were noted to have evidence of renal scarring on ^{99m}Tc-DMSA scintigraphy or on intravenous pyelography one to two years after their first apparent UTI.

Conclusions

Our observations confirm the validity of regular monitoring of children via static renal scintigraphy six months after an APN episode. This monitoring is important in detecting potential renal scarring. While many paediatricians have on occasion encountered a complicated case of UTI where an earlier DMSA scan was, or would have been, helpful in the patient's therapy, timing of examinations and monitoring; such cases are rare and do not warrant changes in the existing investigative algorithm for all children following APN. The six-month protocol is deemed sufficient from the clinical standpoint, while preventing unnecessary radiation exposure to the patients.

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