

Technetium-99m-DMSA Studies in Pediatric Urinary Tract Infection

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Urinary tract infection (UTI) is a common condition in children and may lead to renal scarring with a risk of later hypertension and renal insufficiency. We made a cross-sectional study of the ^{99m}Tc -DMSA findings in 496 children referred for following symptomatic UTI to a Department of Nuclear Medicine and we categorized the results, to provide a framework for further study. **Method:** A standard ^{99m}Tc -DMSA protocol was used to study 496 children (157 males, 339 females) aged from birth to 14 yr. Findings were classified according to the image appearance and relative function of each kidney. These were related to age, sex, history and timing of UTI and the results on micturating cysto-urethrography (MCU). **Results:** Images were normal, with function within normal limits (45%–50% in one kidney), in approximately half the boys and girls studied. The other images were classified as equivocal in 68 children, abnormal unilaterally in 105 and bilaterally in 76, and they were subdivided according to the image appearance. No image changes could be identified that were specifically associated with acute UTI. Diffuse change alone was uncommon. A high proportion of abnormal images was found in infant boys, older girls with recurrent UTI and those children with vesico-ureteric reflux (VUR). Of the bilateral abnormal images, 98% were seen in children with VUR. **Conclusion:** Our findings suggest that infective renal change may be superimposed on underlying congenital lesions (perhaps detectable antenatally) or may be acquired following UTI in the presence of reflux and are thus potentially preventable. This study also suggests that VUR is almost certain to have occurred in a child who has bilateral abnormal ^{99m}Tc -DMSA images following UTI and is also commonly present in those with definite unilateral defects.

Key Words: technetium-99m-DMSA; urinary tract infection; vesico-ureteric reflux; pediatrics

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Urinary tract infections (UTI) are common in children and occur in up to 3% of girls and about 1% of boys. UTI occurs in equal proportions in infancy. They are an important cause of morbidity in childhood but their main significance lies in their association with the renal scarring of reflux nephropathy, which carries a risk of subsequent hypertension and renal failure. Renal scarring has been reported on intravenous urography (IVU) in about 12% of children with UTI and in 25% of those with a recurrent infection; in children it is almost always associated with vesico-ureteric reflux (VUR) (1).

If there is no delay in effective treatment of UTI (2–5), there is real potential for preventing or limiting the acquisition of renal scars. Thus, there is a need for an imaging technique that will identify infants and children who have, or are at risk of, renal damage by detecting either acute renal parenchymal inflammation or the permanent changes due to either congenital renal malformations or acquired renal scars.

Many reports have indicated that ^{99m}Tc -dimercaptosuccinic acid (^{99m}Tc -DMSA) imaging is a sensitive method for investigating children with UTI. This method can identify defects of

function associated with both acute parenchymal inflammation, which can be reversible, and established renal scarring, which will be permanent (6–13). The percentage contribution of each kidney to total renal function can also be determined. The abnormalities observed in ^{99m}Tc -DMSA studies in children with UTI have been classified by several authors (14,15), but the significance of the changes, their predictive value and the clinical role of the ^{99m}Tc -DMSA remains to be determined.

This article presents an analysis based on a cross-sectional study of the ^{99m}Tc -DMSA findings in a population of 496 consecutive children with bacteriologically proven UTI. Abnormal images were typed according to the severity of change and relative function and were analyzed in relation to various parameters including the observation of VUR.

MATERIALS AND METHODS

We studied children with symptomatic, bacteriologically proven UTI referred to the nuclear medicine department at Guy's Hospital between 1985 and 1990 for ^{99m}Tc -DMSA studies. Referrals were made through the Guy's Pediatric Department from general practitioners (24%), or from Guy's Hospital Casualty department (22%) or from other hospitals (54%). Although some patients were under the clinical care of one of the authors, most of these children were cared for by referring clinicians who controlled their subsequent investigation and management. Children with known urinary tract malformations such as duplex or single kidneys or with outflow obstruction were excluded.

Technetium-99m-DMSA imaging was performed using a standard protocol throughout the study period. The radioactivity administered was adjusted using a body surface area correction formula with a minimum administered dose of 37 MBq (16). Either a high-resolution or general-purpose collimator was used and data were acquired in a 64×64 word matrix. Images were obtained in four standard projections 4 hr after injection. Data acquisition in each projection was continued to a total of 650K counts per view. Sedation was available for any distressed child but, with careful preparation of parent and child, it was seldom required.

Renal images were categorized according to the appearance and extent of any functional defect and related to the results of divided function (Fig. 1). A contribution of 45%–50% to total renal function by one kidney was considered normal, while a contribution of 44% or less was regarded as abnormal. Equivocal changes in appearance included minor surface flattening or indentation so that normality was uncertain even after examination of oblique views. Kidneys were classified as small (Types 6, 8, 9) by visual inspection of the image, and if unilateral, by a contribution of 25% or less to total function. Type 7 included all bilateral abnormal images, apart from the small kidneys, though the abnormalities varied in extent.

The findings were analyzed in relation to the age and sex of the child, the previous history of UTI, the timing of the most recent infection and the presence or absence of VUR on contrast micturating cysto-urethrography (MCU). UTI was classified as single when it was the first known and bacteriologically proved, and

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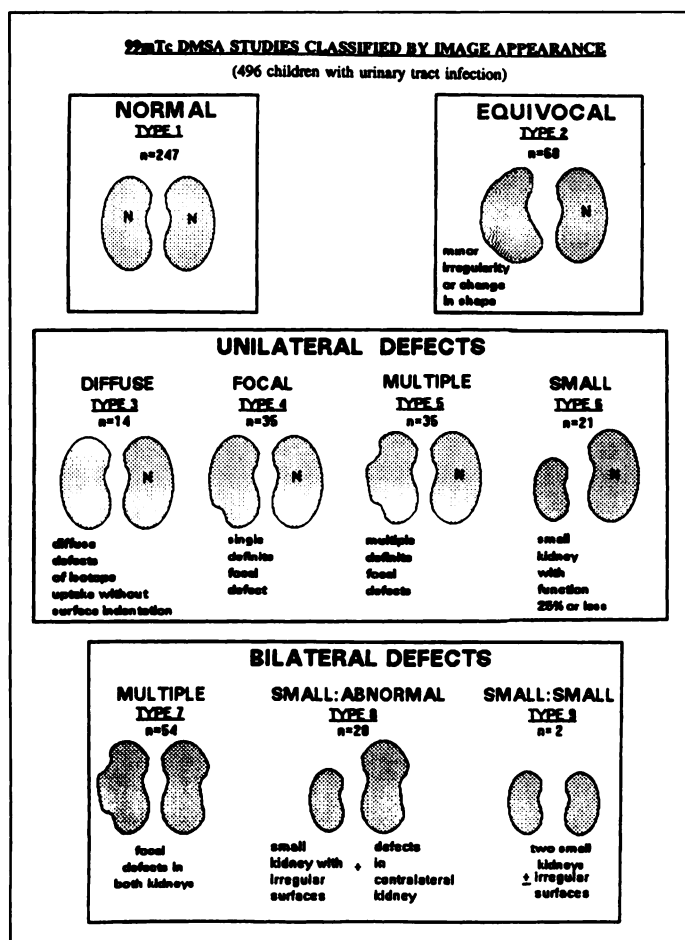


FIGURE 1. Technetium-99m-DMSA studies classified by image appearance in 496 children with urinary tract infection.

recurrent if there was a history of earlier proved or suspected infection.

RESULTS

Of the 496 children studied, 222 children were investigated after the first proven UTI; the remaining 274 children had a history of proven (161) or suspected (113) recurrent symptomatic infection. Technetium-99m-DMSA studies were performed in 132 children within 1 mo after the infection and after longer intervals in the remainder. Cystograms were performed in 361 children (121 boys, 240 girls).

Technetium-99m-DMSA Appearances and Differential Function

In 247 (50%) children the images were normal in appearance and the differential function was within normal limits (Figs. 1, 2 and Table 1). In 86% (212) of these, one kidney contributed 47%–50% of total function. In the 68 children with equivocal image changes, differential function was within normal limits in 53%. Images were definitely abnormal in 181 children; in these, function was within normal limits in 37% of 105 with unilateral defects (Types 3–6), and in 18% of the 76 with bilateral abnormalities (Types 7–9).

Findings in Relation to Sex and Age

Figure 3 indicates that 334 (67%) of the total 496 children studied were under 5 yr of age (61% of the girls and 82% of the boys), and just over a fifth were under 1 yr. Boys represented 58% of the 104 children studied under 1 yr of age, whereas they formed only 18% of the 162 children studied aged 5 yr or over.

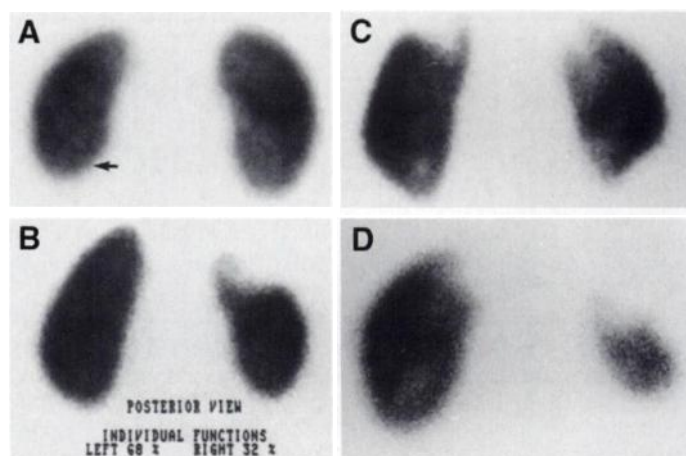


FIGURE 2. Examples of abnormal ^{99m}Tc-DMSA studies (posterior views). (A) Type 2 = equivocal abnormality in left kidney. (B) Type 4 = unilateral focal abnormality. (C) Type 7 = bilateral multiple abnormalities. (D) Type 8 = right small kidney, multiple abnormalities in left kidney.

The normal findings in 247 children comprising 74 (47%) of the boys and 173 (51%) of the girls (Fig. 4), were distributed fairly evenly for age. There were 44%–48% normals in each age group, except for a slightly higher proportion (57%) of normal findings in those aged between 2 and 5 yr.

Twenty-four (35%) of the equivocal changes were seen in boys and 44 (65%) in girls; fewer were seen as age increased, from 18% in those under one to 10% of children aged 5+ yr. The 181 children with definite abnormalities comprised 59 boys and 128 girls. Overall, ^{99m}Tc-DMSA findings were abnormal in 38% of all boys and 36% of all girls studied. There was, however, a preponderance of bilateral abnormalities (Types 7–9) in boys under the age of 1 yr and in girls aged 5 yr and over: 16 of 22 children under 1 yr with Type 7–9 images were boys, half with recurrent infections, while of the 29 children aged 5 yr and over with bilateral abnormal images, 27 were girls, all with recurrent UTI (Figs. 4, 5).

Among the children under 1 yr of age with bilateral abnormalities an abnormal fetal renal tract had been suspected in all four boys who underwent antenatal ultrasonography. Subsequent partial or total nephrectomy in four other boys revealed dysplastic elements in three kidneys and evidence of reflux nephropathy in all four. Only two of the six girls less than 1 yr with bilateral abnormal images underwent antenatal ultrasonography; hydronephrosis was reported in one. Later nephrectomy

TABLE 1
Relationship between Image Appearance and Percentage Contribution of One Kidney to Total Function

DMSA image appearance	Image type	Percent function in one kidney					Total children
		45–50%	40–44%	30–39%	20–29%	10–19%	
Normal	1	247	—	—	—	—	247
Equivocal	2	36	31	1	—	—	68
Abnormal unilateral	3	10	4	—	—	—	14
	4	17	13	3	2	—	35
	5	12	6	11	6	—	35
	6	—	—	3	10	8	21
Abnormal bilateral	7	13	13	22	6	—	54
	8	—	—	4	11	5	20
	9	1	—	1	—	—	2
Total		336	67	45	35	13	496

SEX AND AGE AT TIME OF ^{99m}Tc DMSA STUDY IN 496 CHILDREN WITH UTI

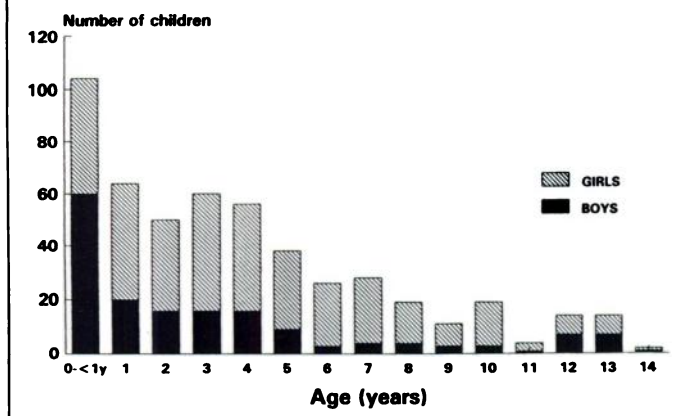


FIGURE 3. Age distribution (range 12 days–14 yr; mean 3.7 yr) and sex in 496 children with UTI investigated with ^{99m}Tc-DMSA.

performed after repeat infections in two other girls presenting under 1 yr showed changes of “reflux nephropathy” in both.

Findings Related to UTI

History of Urinary Infection. Sex distribution, in relation to age and history of UTI is shown in Fig. 5. The proportion of children with a history of recurrent infection rose from 41% (43) of 104 under 1 yr of age to 73% (118) of the 162 children aged 5 yr or over. ($\chi^2 = 24.99$, $p = <0.001$) (Fig. 6). In girls, the proportion presenting with a history of recurrent infection increased with age, whereas this was not seen in boys. Overall, girls formed 75% (206) of the children with a history of recurrent infection compared with 67% of the study population.

A higher proportion of children investigated after recurrent UTI had an abnormal ^{99m}Tc-DMSA study than those investigated after a single infection as seen in Fig. 6. In children aged 5 yr and over, definite abnormal studies were identified in 64 (55%) of the 118 with recurrent infections (bilateral in 28 of them), compared with 7 (15%) of the 44 with presumed first infections (only one with bilateral Type 7 images). ($\chi^2 = 17.6$, $p = <0.001$) Normal images were seen in 133 (60%) of the 222 children with a presumed first and 114 (40%) of the 274 with a recurrent history. ($\chi^2 = 42.1$, $p = <0.001$; trend in mean scores = 33.2, $p = <0.001$).

Findings in Relation to Time of Last Infection. Twenty-seven percent of ^{99m}Tc-DMSA studies were performed within 1 mo after the last recorded urinary infection and nearly 60% within 3 mo. The findings at increasing intervals after the last infection are shown in Table 2. In this population of children no clear relationship could be detected between specific types of abnormal image and the time interval after infection.

Detailed examination of the children investigated within 1 mo of infection showed that Types 4–9 abnormal images were seen in 14 (26%) following a single infection, compared with 37 (47%) of the 79 with recurrent UTI (Table 3).

Findings in Relation to Vesico-Ureteric Reflux

A cystogram was performed in 361 children, 60% within 3 mo before or after the ^{99m}Tc-DMSA. Reflux was seen in 70% of them (Table 4). The images were normal in 147, of whom 59% had demonstrable vesicoureteric reflux (VUR) (43 unilateral, 43 bilateral); they were equivocal in 45, just over half with VUR (8 unilateral, 16 bilateral). VUR had been demonstrated in 142 (84%) of the 169 children with abnormal images; in 72% of the 94 with unilateral ^{99m}Tc-DMSA abnormalities (bilateral in

^{99m}Tc DMSA IN 496 CHILDREN WITH UTI Sex and Age at time of study

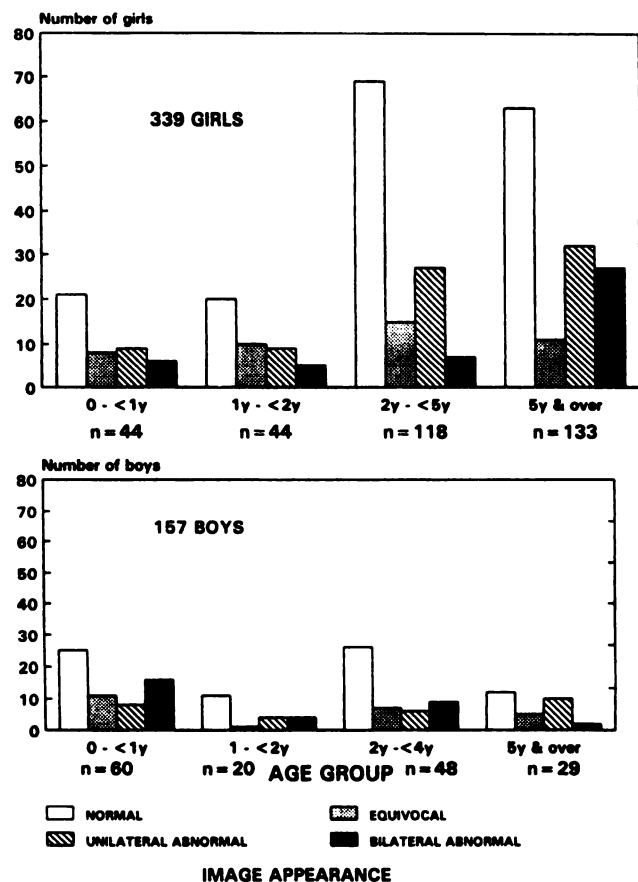


FIGURE 4. Image appearances in 496 children with UTI related to age and sex.

37) and in 74 of the 75 children with bilateral changes (unilateral in 17).

As the severity of ^{99m}Tc-DMSA changes increased, the proportion of children with recurrent UTI and VUR also increased. With unilateral ^{99m}Tc-DMSA changes the proportion with VUR decreased with age: 87% of those under 1 yr with unilateral abnormalities had VUR compared with 68% of those aged 5 yr and over. ($\chi^2 = 1.17$, $p = 0.28$ ns).

UTI HISTORY AT TIME OF ^{99m}Tc DMSA

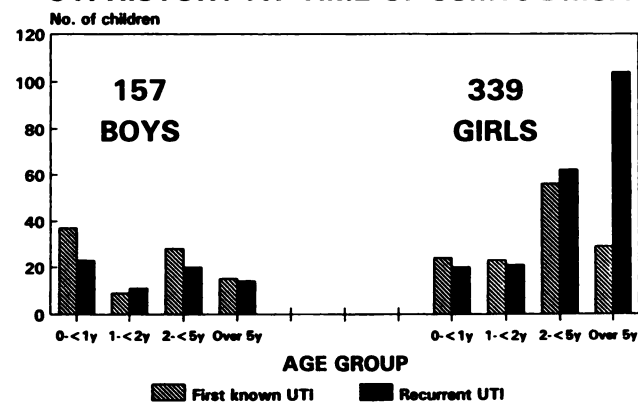


FIGURE 5. History of presumed first or recurrent UTI at time of ^{99m}Tc-DMSA study in 496 children.

99mTc DMSA IN 496 CHILDREN WITH UTI Recurrent and Single Urinary Infection

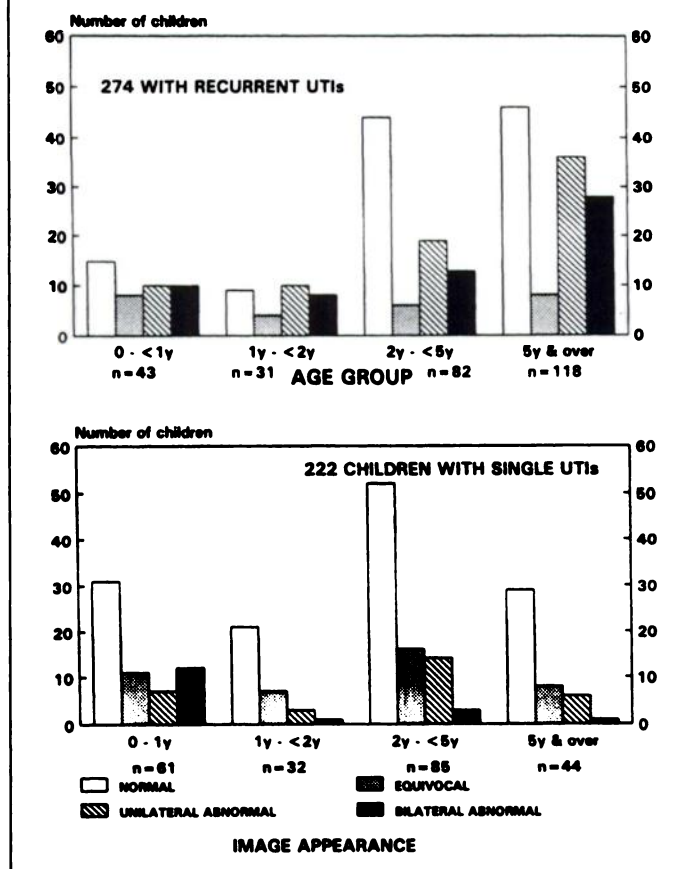


FIGURE 6. Relation of ^{99m}Tc-DMSA appearances to history of first known (222) and recurrent (274) UTI in 496 children.

Individual Kidneys. No reflux was recorded in ureters draining 277 normal kidneys, or 21 with equivocal changes or 23 with definite abnormal images. VUR was reported in association with 182 of the 459 kidneys with normal images, 24 with equivocal changes, 64 of the 68 kidneys with unilateral abnormal images and 131 of the 150 bilateral abnormal renal images. Thirty-nine children had unilateral equivocal or abnormal findings and unilateral VUR which corresponded with the abnormal kidney in all but four.

Children. Of the 252 children with VUR, 16 (76%) of the 21 bilaterally abnormal ^{99m}Tc-DMSA images seen in the first year of life occurred in boys; 10 of these 16 presented with a first infection. In children aged 5 yr and over with bilateral abnormal images and VUR, 27 of the 28 were girls with a history of

TABLE 2
Technetium-99m-DMSA Findings Related to Timing in Months after UTI

Image appearance	Image type	Time of study after infection				Total
		0-1 mon	1-6 mon	6-12 mon	12 mon+	
Normal	1	57	141	31	18	247
Equivocal	2	18	34	10	6	68
Diffuse	3	6	6	—	2	14
Unilateral	4-6	24	43	11	13	91
Bilateral	7-9	27	30	10	9	76
Total		132	254	62	48	496

TABLE 3

Data from Technetium-99m-DMSA Studies in 132 Children Examined within 1 Month after UTI: Relationship to History of Infection

Image appearance	Image type	History of UTI		
		First known	Recurrent	Total
Normal	1	25	32	57
Equivocal	2	10	8	18
Diffuse	3	4	2	6
Unilateral	4-6	6	18	24
Bilateral	7-9	8*	19†	27
Total		53	79	132

*Includes five boys under 6 mo of age.

†Includes four boys under 6 mo of age.

recurrent UTI. Among the 86 children with VUR and normal images, the cystogram in 16 and the last UTI in 13 preceded the ^{99m}Tc-DMSA study by at least 1 yr, so that, in at least 29 of them, transient acute ^{99m}Tc-DMSA changes could have resolved (Table 4). Twelve of the 26 children with unilateral ^{99m}Tc-DMSA abnormalities without VUR were over 5 yr of age when the cystogram was performed. The interval between ^{99m}Tc-DMSA and cystography was 5-18 mo in five others, in two of whom VUR had been suggested by dilatation reported on ultrasonography immediately after UTI.

Where reflux severity was known, a wide spread of image defects was seen in relation to the reflux grade. However, the more extensive ^{99m}Tc-DMSA image defects were usually related to more severe reflux. Such reflux with dilatation was reported in 44% of the children with bilateral image changes, 22% with unilateral abnormal images, 10% with equivocal results and 3% with normal images.

No MCU was recorded in 135 children, 100 of whom had normal ^{99m}Tc-DMSA findings, 23 had equivocal changes and 11 had definite unilateral abnormal ^{99m}Tc-DMSA images.

Abnormal Images (Fig. 1 and Table 1)

The individual abnormal image types are summarized below.

Type 2 (68 children): Equivocal changes occurred in 14% of the population, in the same proportion in girls as in boys. Fewer were seen as age increased, from 18% of those studied under 1 yr to 10% of those aged 5 yr or over; 47% had asymmetrical function; and 53% of the 45 undergoing cystography had VUR, bilateral in two thirds of them.

TABLE 4

Technetium-99m-DMSA Image Appearance in 361 Children with UTI Undergoing Micturating Cystourethrography (MCU)

Image appearance	Image type	Vesico-ureteric reflux						Total
		Not seen			Seen			
Normal	1	61	33 (S)	28 (R)	86	31 (S)	55 (R)	147
Equivocal	2	21	11 (S)	10 (R)	24	12 (S)	12 (R)	45
Abnormal unilateral	3-6	26	9 (S)	17 (R)	68	15 (S)	53 (R)	94
Abnormal bilateral	7-9	1	—	1 (R)	74	17 (S)	57 (R)	75
Total		109			252			361

S = single or first known UTI; R = recurrent UTI.

Type 3 (14 children): Diffuse changes alone were seen in only 14 children (8 girls) and in all age groups with no clear relationship to the time of preceding UTI. Cystography in 12 showed reflux in 8.

Type 4 (35 children): Unilateral single focal defects of uptake were seen almost exclusively in girls (32 of 35); the three boys were under 20 mo. In children over the age of 2 yr, 24 were seen. Fifteen children followed a single known infection. The relative function was normal in half (Table 1). VUR was demonstrated in 20 of the 29 who underwent cystography.

Type 5 (35 children): One abnormal kidney with multiple defects was seen in 28 girls and 7 boys. Children aged 2 yr and over predominated (30), and only 2 (1 boy) were seen under 1 yr of age. UTI had recurred in 30 and was the first known infection in 5. Differential function was normal in 12 of them. VUR was seen in 22 of 32 children undergoing MCU and the 10 in whom it was not demonstrated were mainly 5 yr of age or over.

Type 6 (21 children): Unilateral small kidneys were fairly evenly distributed in relation to age (12 boys, 9 girls). Four (2 under 1 yr of age) were studied after a first known infection. VUR, bilateral in 9, occurred in 18 of 21 affected kidneys. The 3 with no VUR were aged 4, 7 and 10 yr.

Type 7 (54 children): Bilateral abnormal images were seen in 11% of the total population studied. Fifteen were under the age of 1 yr (11 boys, 4 girls) and 21 were aged 5 or over (2 boys, 9 girls); 13 (9 under 1 yr of age) of the 54 were studied after a first UTI and 41 after recurrent infections. VUR was seen in 52 of the 54: one boy aged 9 mo, had no recorded reflux; another had no cystogram.

Type 8 (20 children): Of the children with bilateral abnormalities with one small kidney, 11 were girls; 6 were aged 5 yr and over. The 9 boys were all under the age of 5 yr, 4 under 1 yr of age. All 20 had VUR, bilateral in 19.

Type 9 (2 children): Of the children with bilateral small kidneys, both were girls with bilateral reflux, a history of recurrent UTI and impaired renal function. They were aged 12 and 13 yr; one had been referred for renal transplantation.

DISCUSSION

In this study of the ^{99m}Tc -DMSAs in 496 children there was a preponderance of young children and those under 1 yr, but the median age (3 yr 7 mo) was higher than in some other reports (12,17). The high incidence of severe abnormalities probably reflects the study population which included many referrals from other hospitals.

Image Findings

The findings were normal in appearance and relative function in approximately half of both girls and boys and in a slightly higher proportion of children aged 2–5 yr. However, since there were also severe abnormal changes in this group, diligence in their investigation should not be relaxed.

It was not possible, even with oblique views, to be certain of the normality of the image in 14% of the children and the findings were classed as equivocal. Their significance could not be assessed without follow-up and this will be the subject of a separate report.

Severe bilateral image defects were seen particularly in boys under 1 yr of age and in older girls, associated in both with VUR. Under the age of 1 yr, half of those with abnormal findings were investigated after a single infection. Eight of the 16 boys under 1 yr of age with bilateral abnormal images either had suspected abnormalities on fetal ultrasonography, or dysplastic elements were found in kidneys which were subse-

quently removed. (Eight other male infants, with similar bilateral abnormal renal images [Type 7], had to be excluded from the study because their ^{99m}Tc -DMSA scans, performed after an abnormal fetal scan, had preceded the infection). These observations are consistent with the findings of others (18). For example, Sheridan et al. found abnormal ^{99m}Tc -DMSA images in two thirds of boys under 6 mo of age following UTI and one third of those without UTI, following abnormal fetal ultrasonography (19), while Risdon et al. demonstrated dysplastic elements in 63% of kidneys removed from 34 boys aged less than 1 yr of age (20). These findings and those of our study support earlier clinical observations (21) and the view that infective renal damage may be either superimposed on congenitally malformed kidneys, usually in association with VUR, or may be acquired in previously normal kidneys, the latter more frequently in girls with VUR who themselves are more prone to recurrent UTI (22). More than 90% of the abnormal findings in children of 5 yr and over were seen in those with a history of recurrent infection, mainly girls, emphasizing the importance of rapid treatment and investigation of first infections.

Acute Technetium-99m-DMSA Changes Following UTI

Both clinical and experimental studies indicate that prompt antibacterial treatment of an acute UTI will encourage the resolution of acute renal lesion and limit or prevent its progression to scarring (2–4,7,23). Clinical management can be guided by early recognition of renal involvement during acute UTI which is not reliably detected by ultrasonography (24–27), and is often overlooked on intravenous urography (IVU) (28). The functional defects on ^{99m}Tc -DMSA scintigraphy provide a more sensitive indication of renal involvement (6,7,10,29,30).

Diffusely reduced tracer uptake without surface indentation (Type 3) at the presumed site of infection which has been widely reported following acute UTI (6,7,24,29), was uncommon in our study and distribution of this finding in relation to the time interval after infection was similar to that of other abnormal images, even when first known infections investigated within one month were considered. The probability that acute UTI may be followed by focal segmental changes will be further explored on follow-up. Since some infective renal involvement is likely to be superimposed on dysplastic renal elements, it is not surprising that even ^{99m}Tc -DMSA studies carried out within one month of UTI varied widely in appearance.

Timing of Study

The most appropriate time for performing ^{99m}Tc -DMSA imaging after a proven UTI remains uncertain. If carried out immediately all those at risk including those with unsuspected underlying abnormalities will be identified rapidly and appropriate early management can be introduced. Twenty percent of the 132 studied within a month of the presenting UTI had bilateral abnormal images (Types 7–9), 42% of these following a first known infection, raising the possibility that either the abnormalities were present at birth or that a preceding infection was unrecognized.

Associations with VUR

We confirmed the close relationship between abnormal ^{99m}Tc -DMSAs and VUR reported by others (13,31). However, this is contrary to the recent experience of some groups, particularly following acute UTI (32,33) and requires further exploration. In our study, when image abnormalities were bilateral, VUR had been demonstrated in 99% of children undergoing cystography and reflux was bilateral in 77%. VUR was recorded in 72% of children with a unilateral abnormality;

the trend towards less VUR being seen in older children than in the very young corresponds to the natural resolution of VUR with time which is more likely to occur when VUR is unilateral (34,35). Since it is well known that after the newborn period a past history of UTI is difficult to exclude, our findings indicate that early investigation by ^{99m}Tc -DMSA is advisable at any age. Delaying the ^{99m}Tc -DMSA for several months should theoretically allow acute changes to subside thus avoiding confusion with defects due to permanent renal scarring but we consider that the clinical advantage of early identification of those at risk outweighs the disadvantages.

A higher proportion of abnormal radioisotope findings was seen in the group undergoing MCU than in the total study population because a clinical decision had been made not to perform an MCU in 100 children with normal ^{99m}Tc -DMSA studies, many with a single infection.

Apparent discrepancies were seen in 16% of children with definite abnormalities but no demonstrable VUR at the time of study, and 47% of children with equivocal ^{99m}Tc -DMSA images. This might be explained by the natural tendency for VUR to resolve. There were only 10 children under the age of 5 who had abnormal ^{99m}Tc -DMSA studies without VUR in whom there was no significant delay between ^{99m}Tc -DMSA and MCU. Furthermore, 58% of children with normal ^{99m}Tc -DMSA studies had demonstrable VUR. There are several possible explanations for this. The infecting organism may have been non-nephropathic, or compound renal papillae allowing intrarenal reflux (36) may have been absent, or during the time interval between UTI and the ^{99m}Tc -DMSA study, post-treatment resolution of acute inflammation may have occurred.

CONCLUSION

This study indicates that after UTI a wide range of ^{99m}Tc -DMSA images can be seen, throughout childhood, and in a similar proportion of boys and girls. Abnormal images were seen particularly in boys under 1 yr of age and in girls presenting with recurrent UTI aged 5 yr or over. No specific changes following acute infection were identifiable. Investigation is thus important at all ages. VUR was almost invariably present, and should be sought, in children with bilateral ^{99m}Tc -DMSA abnormalities. The significance and potential for resolution of equivocal and abnormal ^{99m}Tc -DMSA images will depend upon the child's clinical progress and will emerge from follow-up studies and comparison with other imaging.

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