Original articles

Serial ^{99m}Tc dimercaptosuccinic acid (DMSA) scans after urinary infections presenting before the age of 5 years

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SUMMARY Forty five children presenting with a first proven urinary tract infection under the age of 5 years were studied by sequential ^{99m}Tc dimercaptosuccinic acid (DMSA) scans. Forty nine kidneys in 40 children had definite defects at presentation, and 39 (80%) of these defects were still present when the DMSA scan was repeated. Changes in the appearance of defects were independent of the presence or degree of reflux at presentation and of symptomatic recurrence of infection, though the combination of new infection and grade 3 reflux (reflux reaching the renal calices with distension) was associated with deterioration. No kidney with a relative DMSA uptake of less than 35% showed any improvement in its cortical defects. Only two kidneys that were initially without defects, in a single patient who had bilateral grade 3 reflux and breakthrough infections, developed defects on subsequent scans.

The outcome after urinary tract infection is dependent on the effect of the first infection on the kidney. Occasionally children with grade 3 reflux develop damage during subsequent infections. More widespread use of DMSA scans should improve our understanding of the factors that determine the development of renal damage.

Urinary tract infections in young children, particularly when they are associated with vesicoureteric reflux, can lead to renal scarring^{1 2} and subsequently to renal dysfunction and hypertension.³ The difficulty of recognising vesicoureteric reflux before the first urinary tract infection has focused attention on the prevention of new scarring after the first infection.⁴ It is uncertain how much scarring is sustained at the time of first infection, and how much is the result of repeated infections and thus (in theory) preventable. Serial studies of kidneys have used excretory urography^{5 6} but as this technique can take up to two years to show the full extent of scarring^{6 7} it makes the positive identification of new scars difficult. ^{99m}Tc dimercaptosuccinic acid (DMSA) scans are more sensitive for detecting early renal defects, especially in the under 5 age group,^{8 9} and the relative uptake of DMSA can be measured to give an objective measurement of renal function in unilateral damage. The appearance of new defects on subsequent scans is likely to be due to new lesions rather than the contraction of original scars by fibrosis, as shown by excretory urography.

We have now carried out second DMSA scans on 45 children who were originally scanned shortly after a first urinary tract infection, and we report the changes.

Patients and methods

Over a three year period (1982–4) 115 children under the age of 5 years presented with a symptomatic, microbiologically proved, urinary tract infection. None of the children had a history of previous urinary tract infections or of recurrent fevers of unknown origin. A DMSA scan was performed as part of an investigation protocol that also included intravenous urography and ultrasonography, and micturating cystourethrography in selected patients. The methods and the results have been reported previously.⁹

Thirty nine of the 115 children, and a further six children seen since 1984 who also presented with a first symptomatic urinary tract infection, have now had further DMSA scans and this was the criterion for inclusion in this study. The decision to repeat the

scan was taken on clinical grounds by the child's clinician, and reasons included an abnormal first DMSA scan, and detection of vesicoureteric reflux or further urinary tract infection, or both. There were 15 boys and 30 girls. All of them had had a micturating cystourethrogram and a DMSA scan within a month of presentation. In addition all had either an ultrasound scan or an intravenous urogram, and 18 had both.

The mean age at the time of the first scan was 2.04 years (range 12 days to 4.9 years) and at the time of the second scan 4.29 years (range 33 weeks to 9.5 years). The mean interval between scans was 2.25 years (range 25 weeks to 6.3 years).

Reflux seen on the micturating cystourethrogram was recorded on a scale of 1 to 3 (grade 1—confined to the ureter; grade 2—reaching the renal calices, without distension; and grade 3—reaching the renal calices, with distension). All children with reflux received continuous prophylactic antibiotics in the period between the two DMSA scans or, in 17 cases where reflux was corrected surgically, until six months after operation.

The results of the DMSA scans were reviewed without knowledge of other imaging results or of the clinical course. Each kidney was classified as being abnormal (showing a definite cortical defect or having diffuse abnormality of DMSA uptake), as having a possible cortical defect, or as being normal. The finding of diffuse abnormality was recorded independently of the relative percentage uptake. The kidneys on the second scan were similarly classified and in addition assessed as deteriorated, unchanged, or improved, compared with the first scan. Relative DMSA uptake was measured in 89 of the 90 scans performed.

Results

In the 45 children the initial cystogram showed 15 had no reflux, 11 had unilateral reflux, and 19

bilateral reflux. Of the 49 refluxing kidney units eight had grade 1, 18 had grade 2, and 23 had grade 3 reflux. Seventeen children had operations to correct reflux in 27 kidneys, including 12 with grade 3 reflux. Cystography was not repeated as part of the study except when clinically indicated (when operation was being considered or before stopping antibiotic prophylaxis).

KIDNEYS THAT INITIALLY SHOWED DEFINITE ABNORMALITIES

Forty nine kidneys in 40 children initially showed abnormalities. Forty of them (80%) still showed defects at follow up. Eight defects were improved but still definite, 28 were unchanged, and four had deteriorated. The remaining nine kidneys had no defects at follow up. The time between scans in this group was significantly shorter than in those kidneys where the defects persisted (median time 0.7 years compared with 2.5 years, $p < 0.01$ Mann-Whitney U test). None of the children whose renal defects resolved had breakthrough infections compared with 11 in children with persisting defects. This difference was not significant. There was no association between changes in the appearance of the kidneys on the DMSA scans and the presence or degree of reflux at presentation.

KIDNEYS THAT INITIALLY SHOWED POSSIBLE DEFECTS

Nine kidneys initially showed possible defects. The uptake of DMSA in those with contralateral normal kidneys was in the normal range of 43–57% (median 50.5%) and was significantly higher than kidneys with definite defects (median 40% $p < 0.01$ Mann-Whitney U test). Three of the defects had disappeared on subsequent scanning, and the six that persisted remained equivocal, none showing deterioration into definite defects. For the purpose of this analysis we have reclassified these kidneys as normal and included them with the 32 kidneys with no defects.

Table 1 *Change in appearance of scan in 90 kidneys*

Outcome	Breakthrough infection (n=26)		No breakthrough infection (n=64)		Total
	Reflux (grade 3)	No reflux (reflux surgically corrected)	Reflux (grade 3)	No reflux (reflux surgically corrected)	
No defect on either scan	4 (1)	7 (2)	3 (1)	25 (7)	39
Resolved or improving defect	2 (2)	0	2 (0)	13 (4)	17
Unchanged defect	2 (2)	7 (6)	5 (1)	14 (8)	28
Deteriorating defect	1 (1)	1 (0)	1 (1)	1 (0)	4
New defect	2 (2)	0	0	0	2
Total	11 (8)	15 (8)	11 (3)	53 (19)	90

KIDNEYS THAT INITIALLY LOOKED NORMAL

Forty one kidneys initially looked normal; five children had two normal kidneys and 31 had one normal kidney. Thirty two kidneys had no reflux, or reflux that was subsequently surgically corrected, and seven of these had been exposed to breakthrough infection. Three kidneys had uncorrected reflux (two had grade 2, and one had grade 3) but there were no breakthrough infections. None of these 35 kidneys developed defects. Six kidneys had breakthrough infections in the presence of reflux (three had grade 1, and three had grade 3). Two of these latter kidneys (in the same child) developed widespread defects.

The outcome in the 90 kidneys is shown in table 1. There was no correlation between changes in appearance between the two scans and the presence of reflux alone, or in the occurrence of breakthrough infection alone, but kidneys with grade 3 reflux and breakthrough infection were at greater risk of deteriorating (three of eight kidneys) than those without this combination (three of 82) ($p=0.001$, Fisher's exact test, two tailed).

CHILDREN WITH UNILATERAL DEFECTS

When one kidney was normal by all imaging techniques (DMSA scan together with intravenous urography or ultrasound scan, or both) it was reasonable to assume that this kidney was also functionally normal and therefore any reduction in relative DMSA uptake by an affected contralateral kidney was considered to indicate an absolute loss of function. There were 30 children with abnormal DMSA scans of one kidney who met this criterion and in whom the divided DMSA uptake was measured. There was a close association between DMSA uptake in kidneys at the first and at the second scan (figure) indicating that the lesion sustained at the first infection was the main determinant of functional outcome.

There was no difference in mean relative uptake

of DMSA at the first scan in kidneys with all grades of reflux ($n=16$, median 39%), or with grade 3 reflux ($n=9$, median 40%), compared with those without reflux ($n=14$, median=42.5%).

There was no difference between the mean relative uptake by kidneys at the first scan and the subsequent scan either in the group as a whole or when they were classified by the presence or degree of reflux, or the occurrence of breakthrough infection during the follow up period (table 2).

There was a significant difference between the initial mean uptake of DMSA by those kidneys in which cortical defects subsequently improved compared with those that showed no improvement ($p<0.05$, Mann-Whitney U test). No kidney with an uptake of less than 35% showed any improvement of associated cortical defects.

Figure DMSA uptake at first and subsequent scans in kidneys with unilateral renal defects ($n=30$). Solid line, $x=y$ ($r=0.938$, $p<0.001$); dashed line, lower limit of normal (42% uptake).

Table 2 DMSA uptake at first and subsequent scans in 30 kidneys with unilateral defects

	No of kidneys	Mean percentage uptake		Difference between means	SEM	p Value
		First scan	Second scan			
Breakthrough	7	36.3	36	0.29	2.14	>0.8
All reflux	8	41.6	40.1	-0.25	1.96	>0.9
Grade 3 reflux	5	39	38.8	0.2	3.18	>0.9
Grade 3 reflux plus breakthrough	3	42.3	43	0.66	1.46	>0.6
All kidneys	30	37.2	38	0.76	0.73	>0.3

Reflux includes only those that were not surgically corrected.

Discussion

When cortical defects are present on initial DMSA scans there is a high risk of permanent damage to the kidney. It has been suggested that some defects seen on scans carried out within three months of a urinary tract infection may be transient¹⁰ and this has led to the idea that scans should not be carried out within this period.¹¹ In our series 80% of such changes persisted. We believe that waiting for three months before carrying out a scan is undesirable, as it will result in delay in identifying children with kidneys at risk.

The transient defects probably represent focal bacterial nephritis that resolves; recent experimental work has shown that kidneys with defects on DMSA scan after infection and reflux always have a corresponding pathological lesion, but this is not always permanent.¹²

We examined the hypothesis that defects may disappear when there is a long interval between the scans, but—on the contrary—the findings showed that these children had been rescanned at shorter intervals than those children whose defects persisted and that disappearance of defects would therefore seem to be independent of the interval between scans.

The follow up scans showed that equivocal cortical defects are unlikely to be associated with long term renal damage. This makes the scans easier to assess, as minor variations in cortical outline (which may represent fetal lobulation) can be interpreted as normal by the radiologist.

This series has confirmed that kidneys that were not damaged by a first infection may occasionally develop appreciable scarring after subsequent infections as has been previously described,^{5,6} but in our series this was only seen in one child who had bilateral grade 3 reflux. The reason that we found so few new scars might be because DMSA scanning is more sensitive in detecting initial parenchymal changes than intravenous urography, upon which earlier studies depended.⁵

Most renal defects remained unchanged regardless of features on presentation or the subsequent clinical course. This suggests that for most kidneys the initial infection determines the subsequent degree of damage, and later breakthrough infection makes little difference if grade 3 reflux is not also present. This supports the work of Ransley and Risdon, who suggested that those kidneys susceptible to parenchymal infection because of their papillary morphology will become damaged at the first infection (the so called 'big-bang' theory).¹³

Where renal damage was unilateral, the initial relative DMSA uptake was a useful guide to later

outcome, and no kidney with a relative uptake of less than 35% recovered. When relative uptake was in the accepted normal range (43–57%¹⁴), however, kidneys could show either temporary or permanent defects. There are limitations to the use of relative DMSA uptake because ipsilateral deterioration cannot be distinguished from contralateral compensatory hypertrophy¹⁵ and the measurement is of little value in the presence of bilateral disease. The recently described technique for measurement of absolute uptake of DMSA in each kidney will allow more precise quantitation of the progress of an individual kidney and allow functional assessment of bilateral impairment.¹⁴ An interesting feature of our original cohort was the high incidence of defects in the absence of reflux.⁹ Twelve of these 26 kidneys had persistent defects on repeat scans, in six the defects improved, and eight have not been rescanned. Assuming that there were no false negative micturating cystourethrograms, this suggests that at least 18% of permanent renal defects develop in the absence of reflux compared with the 2% previously reported in a study in which intravenous urography was accepted as the standard.¹⁶

Further studies of the genesis of renal scarring by DMSA scans, including measurement of absolute DMSA uptake, will improve our understanding of the factors that determine the development of chronic pyelonephritis. The present uncertainty about the natural history of renal scarring is resulting in a worrying lack of consensus among paediatricians about the investigation and management of urinary tract infections.¹⁷ More widespread availability and use of DMSA renal scans should help to resolve some of the unanswered questions.

We thank the consultant paediatricians of Merton and Sutton, mid Surrey, and east Surrey health authorities for referring their patients for investigation, and Dr VR McCready and the staff of the department of nuclear medicine, Royal Marsden Hospital, for carrying out the scans.

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Accepted 23 June 1989