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The significance of a defect on DMSA scan in children with renal transplants

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Abstract: Since December 1995, pediatric renal transplant recipients in our unit have received a DMSA scan as soon as possible post-transplant in order to provide a baseline for comparison in the event of subsequent complications. We retrospectively reviewed the case notes and DMSA scans of the 45 patients who underwent a scan within 9 wk of their transplant to see if pre or peri-transplant factors or post-transplant complications were associated with defects on scanning. Forty percentage of scans had defects. The presence of defects was not associated with potential predisposing factors such as patient or donor age, cadaveric or live donation, cold ischemia time, multiple donor vessels, the use of non-heart beating donors, the mean time to scan, the serum creatinine, or the presence of structural renal tract anomalies predisposing to UTI. However, 87% of patients had complications before the scan, including UTI, rejection, acute tubular necrosis, transplant biopsy and drug toxicity. Children with no clinical complications had a significantly reduced risk of a defect ($p = 0.035$), while biopsy was associated with the presence of defects ($p = 0.0034$). Twenty patients had one or more follow up DMSA scans: one patient developed a new focal defect. In conclusion, renal transplant defects are frequently found on DMSA scanning even early after transplantation and are non-specifically associated with many different complications.

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The development of renal parenchymal scarring, particularly if progressive, suggests a poor graft prognosis. Identification of its cause is important for successful management. UTI is a well documented cause of renal scarring; UTIs develop in approximately one third of children post-transplant (1). In order to ascertain whether renal damage has occurred following a UTI, DMSA, which is taken up by the proximal tubular cells of the renal cortex, may be used to look for parenchymal defects. UTI that has resulted in renal scarring needs thorough investigation to prevent recurrence. However, DMSA is not specific for damage resulting from infection, but may be because of any process that causes parenchymal loss. This might include pre-existing damage to the transplanted kidney, damage during harvesting and subsequent transplantation, prolonged cold ischemia time, the presence of multiple renal arteries predisposing to cortical loss, venous thrombosis, and acute and chronic rejection as well as UTI.

Since 1995, we have undertaken a DMSA scan as soon as possible post-transplant in order to provide a baseline for comparison in the event of subsequent complications. We report the results of these scans, and the results of follow up scans when undertaken.

Abbreviations: ATG, anti-thymocyte globulin; ATN, acute tubular necrosis; CRF, chronic failure; CyA, Cyclosporin A; DMSA, technetium-99m-dimercaptsuccinic acid; HUS, hemolytic uremic syndrome; LRD, live related donor; UTI, urinary tract infection.

Patients and methods

Patients

Between December 1995 and December 1999, 77 patients underwent 79 renal transplants. Sixty nine (87%) were first grafts; eight (10%) were second grafts and two (3%) were third grafts. Forty five patients (57%) had a baseline DMSA study within 9 wk of transplantation (mean 28 days, range 5–9 wk). These patients were included in the analysis. Thirty four patients were excluded because they did not undergo a

Table 1. Complications that occurred before the first scan. Total number of patients 45

Complication	Number	Percentage
No complications	6	13.3
UTI	12	26.6
Rejection episode	35	77.7
Acute tubular necrosis / cortical necrosis	5	11.1
CyA or tacrolimus toxicity	12	26.6
Biopsy	10	22.2
Bladder abnormality	27	59.9

baseline study within 9 wk post-transplant (n = 20). This was because of early graft loss (n = 10), logistical reasons (n = 6) and needle phobia (n = 4). Twenty of the baseline study group (44%) underwent 26 follow up studies at a median (range) of 18.5 (2–132) wk after the baseline scan.

Of the 45 patients included in the analysis, 35 (78%) were male and 10 were female (22%). Their mean (range) age was 9.7 (1.5–17) yr. Causes of CRF were dysplasia with or without reflux (40%), posterior urethral valve (18%), nephrotic syndrome (13%), glomerular disease (7%), neuropathic bladder (4.5%), prune belly (4.5%), reflux nephropathy (2%) and miscellaneous (11%). Immunosuppression was with Prednisolone, Cyclosporin and Azathioprine (n = 37) or Prednisolone, Tacrolimus and Azathioprine (n = 8). All second and third grafts were given ATG or Orthoclone OKT3 in addition to triple therapy. UTI was defined as $>10^5$ cfu/mL of a single organism; rejection as an episode treated with high dose steroid therapy by the attending physician; and CyA/Tacrolimus toxicity was diagnosed by the attending physician or high blood trough levels >250 mcg/L and >15 mcg/L respectively.

Thirty four transplants were from cadaveric donors and 11 were from LRD. The mean (range) age of the cadaveric donors was 19 (4–52) yr and 44 (27–52) yr for the LRD. Three cadaveric donors were non-heart-beating. The mean (range) cold ischemia time was 22.5 (11.6–40.9) h for the cadaveric and 4.0 (2.9–5.1) h for the LRD transplants. There was no history of UTI in any donor.

The children were divided into groups on the basis of their clinical course before the baseline scan. Complications were found to be common (Table 1). Some children had more than one complication.

Methods

The patients received 100 MBq Tc 99m DMSA scaled according to body weight as recommended by the European Association of Nuclear Medicine. Between 2 and 4 h post-injection, posterior, anterior, left and right oblique views were obtained in anterior and posterior projections. Images were acquired for 200 000–500 000 counts using a high-resolution collimator, and a matrix size of 256 × 256. All studies were stored on optical disc and analysed by two experienced Radiologists/Nuclear Medicine physicians who had no knowledge of any clinical or laboratory data. Defects located either peripherally or centrally on any view were recorded. The follow-up studies were compared with the previous images for change. An example of a normal scan is shown in Fig. 1, and of a scan with a defect is shown in Fig. 2.

The following information was obtained from the notes: recipient age and diagnosis, donor age and type, number of donor vessels, cold ischemia time, UTIs, rejection episodes, creatinine level at the time of the scan, biopsies, and Cyclosporin/Tacrolimus levels.

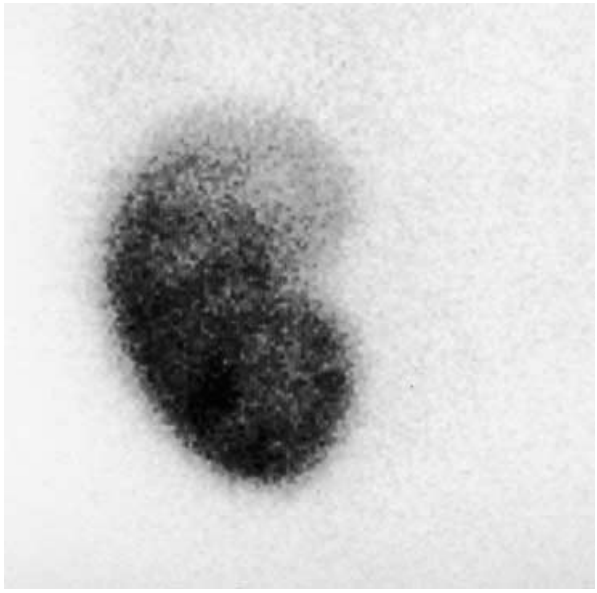

Fig. 1. Normal appearances of the transplant kidney on the anterior view. Note the normal cool pyramids with higher uptake in the renal cortex. There is better uptake in the lower portion of the kidney on this view because the location of the kidney makes the lower pole closer to the anterior surface than the posterior surface.

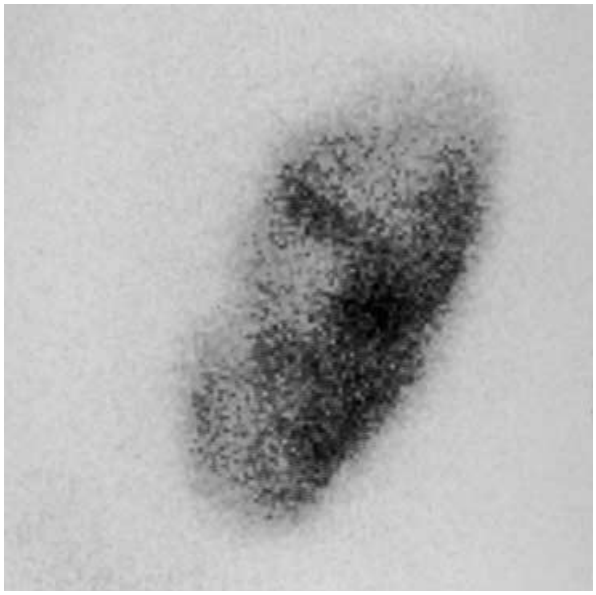

Fig. 2. Following a UTI, there is a defect on the lateral aspect of the kidney on this anterior view.

Statistics

Differences in the presence of parenchymal defects on DMSA between groups were compared for significance using chi-square and logistic regression. Baseline DMSA scans results were correlated with clinical complications,

either between transplant and the DMSA scan or at the time of the scan. Because many of the children had more than one complication, groups were looked at individually and in combinations for significance. The effect of cold ischemia time was assessed using Levene's test for equality of variances. Significance was defined as $p < 0.05$.

Results

Factors associated with the presence of defects on DMSA scan (Table 2)

Eighteen (40%) of the transplanted kidneys had a parenchymal defect at the time of the first scan. The ages of the patients and donors; the serum creatinine at the time of the baseline scan; the number of graft losses; the number of cadaveric donors and LRD; the percentage of children with structural renal tract anomalies predisposing to UTI; the cold ischemia times; the presence of multiple vessels; the number of non-heart beating donors; and the mean time to scan did not correlate with the presence of defects (p = NS for all).

Table 2. Clinical details of the patients with and without focal defects on DMSA scan

	No defects n = 27 (60%)	Defects n = 18 (40%)
Patient age (yr)	9.7 (1.4–15.9)	10.1 (1.5–14.9)
Donor age (yr)	23.1 (4–52)	23.6 (8-52)
Serum creatinine at scan (umol/L)	88 (31–303)	105 (40–210)
Failed grafts	3 (11)	3 (16)
Cadaveric donors (n = 34)	21 (78)	13 (72)
Living related donors (n = 11)	6 (22)	5 (28)
Structurally abnormal renal tracts	20 (74)	12 (67)
Cold ischemia time (cadaveric) (h)	24.8 (12.1–40.9)	19.3 (11.6–36.3)
Cold ischemia time (LRD) (h)	3.8 (3.1–4.5)	4.3 (2.9–5.1)
Multiple donor vessels	6 (22)	4 (22)
Non heart beating donors	2 (7.4)	1 (5.5)
Time to baseline scan (wk)	4.0 (1–9)	3.7 (1–8)

Table 3. Baseline DMSA scans results and clinical complications, either between transplant and the DMSA scan or at the time of scan. Some patients fell into one or more of the groups

Clinical condition	Number	No parenchymal defects	Parenchymal defects	p-value
Group 1 – no complications	6	6	0	0.035
Group 2 – UTI	12	6	6	NS
Group 3 – rejection episode	35	19	16	NS
Group 4 – ATN/cortical necrosis	5	1	4	NS
Group 5 – CyA or tacrolimus toxicity	12	5	7	NS
Group 6 – biopsy	10	2	8	0.0034
Group 7 – bladder abnormality	27	16	18	NS

Table 4. Follow up DMSA scan results correlated with clinical course (n = 20)

Clinical condition between baseline and follow-up scan	No Parenchymal defects		Parenchymal defects	
	First scan	Follow up	First scan	Follow up
UTI	6	**5**	6	**7**
Rejection	6	**5**	7	**8**
CyA/tacrolimus toxicity	1	1	1	1
Biopsy	3	3	5	5

Effect of complications on the presence of defects on DMSA scan (Table 3)

Defects were seen in association with rejection, UTI, ATN and cyclosporin/tacrolimus toxicity.

Children with no clinical complications had a significantly reduced risk of a defect ($\chi^2 = 4.6$ with 1 d.f., $p = 0.035$). Biopsy was associated with the presence of defects ($\chi^2 = 8.57$ with 1 d.f., $p = 0.0034$, Fisher exact test = 0.0079). The biopsies were performed between 5 and 46 days (median 7.5 days) pre-DMSA scan. The two patients who received a biopsy but did not have a defect had their biopsies 7 and 46 days pre-DMSA. Results of biopsies showed: non-specific changes (n = 4), ATN (n = 4), rejection (n = 1) and HUS (n = 1). However, 10 patients had defects but had not received biopsies.

Follow-up scans (Table 4)

Twenty patients (10 with and 10 without defects on the baseline scan) underwent 26 follow up scans: 16 because of UTI; seven because of renal dysfunction; and three were follow up because of an abnormal baseline scan. Only one patient had developed a new defect. She had had both a UTI and rejection (Fig. 3).

Discussion

We have shown that there is a high incidence of focal defects on DMSA scanning in kidneys transplanted into children, even within the first 9 wk post-transplant. Although our rate of 40% of transplants with defects is comparable with previous publications, in no others studies have DMSA scans been performed so early in the post-transplant course (2, 3).

Despite undertaking the scans within a short time of the transplant, already a significant proportion of the children had experienced complications such as ATN, rejection, drug nephrotoxicity, UTI and renal biopsy. We were, therefore, unable to distinguish between damage that had been sustained pre- or peri-transplant,

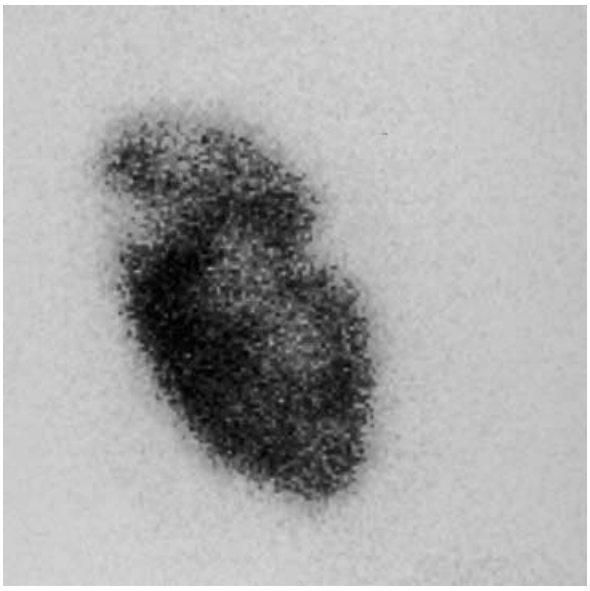

Fig. 3. This child had both a UTI and an episode of rejection prior to the DMSA scan. The right anterior oblique view of the DMSA scan revealed a defect in the upper outer aspect of the kidney.

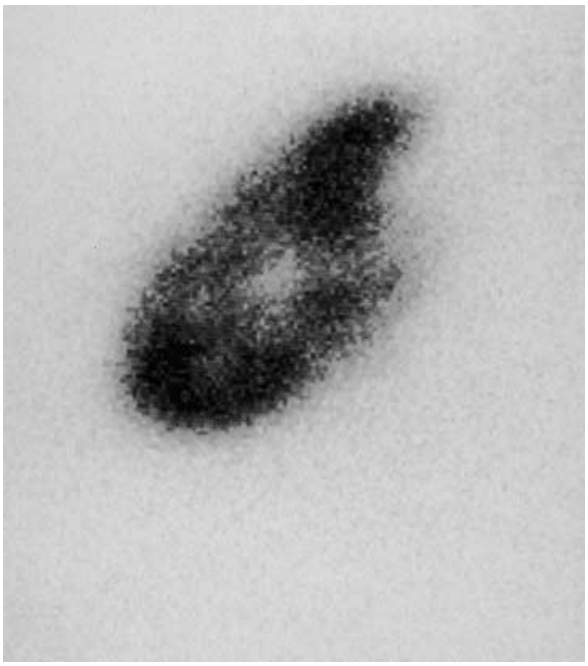

Fig. 4. This child had proteinuria, UTI, rejection and biopsy following the transplant prior to the DMSA scan. The right anterior oblique view shows a defect in the upper pole of the kidney. The defect in the centre of the kidney was because of mild pelvic dilatation.

and damage that occurred after transplantation. Williams found defects in 47% of 19 children (2). There was a correlation between the presence of defects and cold ischemia time, and multiple defects were present in four of the five children with two renal transplant arteries. However, these studies were undertaken at a variable time period post-transplant, and some many months post-transplant. In our study we were unable to show specific effects of cold ischemia time, multiple donor vessels, cadaveric or live donation, or the use of non-heart beating donor, whereas children who did not experience any of these complications did not have transplant defects, regardless of potential pre- or perioperative predisposing causes.

Budihna undertook DMSA scans 1–97 months post-transplant, and found a much higher incidence of DMSA abnormalities (4). Seventy percentage had multiple, patchy areas of decreased activity radiating from the calyces to the cortex. Of these, 43% had focal defects. He found that the time lapse between transplantation and scanning was longer in those with defects, and was higher in those that had experienced acute rejection episodes. Although we were unable to demonstrate en effect of acute rejection, scans in our study were undertaken much earlier.

We, as well as others (3), have shown that there are many different complications associated with defects on DMSA (Fig. 4). This is not surprising because DMSA is taken up by the proximal tubules of the kidney and requires, therefore, that there are patent vessels supplying the tubules and that the tubules are functioning normally. ATN, pyelonephritis, acute and chronic rejection and drug toxicity cause both vascular and tubular lesions which may lead to tubular loss, fibrosis and areas of hypoperfusion. Although DMSA imaging does not help in determining the aetiology of transplant injury, it does enable an estimation of its extent.

The best established use of DMSA is in the investigation of UTI. We were unable to show an effect of UTI on graft scarring, although the one child that went on to develop a scar on follow-up imaging in our study had a UTI. DMSA scanning is well recognized to be useful in the detection of scarring following pyelonephritis, and in the assessment of transplant dysfunction in patients with lower urinary tract abnormalities (5, 6).

DMSA scanning has been demonstrated to be useful in the investigation of hypertension in pediatric transplant recipients. If SPECT imaging is used, it is also possible to identify unsuspected renal infarcts (7). As our scans were performed soon after transplant, we were unable to study the effect of hypertension. This is because in the immediate post-transplant period,

the majority of children are hypertensive because of the large doses of steroids and high fluid intake that are given after the transplant surgery.

We found a significant correlation between renal biopsy and defects. It is not clear if the defect was caused by the biopsy or a result of the disorder that necessitated the biopsy. Biopsy results were variable. Garin compared the results of DMSA with transplant biopsy in 13 patients with impaired renal function. He found defects on DMSA in patients with rejection and drug nephrotoxicity, although some of the patients with defects had normal biopsies and some with no defects had rejection and drug toxicity (3).

In conclusion, renal transplant defects are frequently found on DMSA scanning. The causes are difficult to identify and likely to be multifactorial. An early scan, preferably within the first 3 wk of the transplant, provides a baseline, which may sometimes help in the assessment of future complications.

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