Abnormal Cortical Appearances in Pediatric Renal Allografts

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Renal cortical studies were performed in 19 children with renal transplants. There were 10 normal studies and 9 abnormal studies, 8 of which showed multiple large focal peripheral cortical defects. The following factors showed a positive correlation: (a) the ischemia time of the transplant kidney was significantly shorter in patients with normal studies; (b) cadaver grafts were more likely to have abnormal scan appearances than living related donor grafts; and (c) in four of the five patients with double renal arteries, the scans were abnormal in multiple sites. A possible pathophysiologic mechanism to explain these scan appearances is asymptomatic segmental graft infarction secondary to progressive vascular disease. These infarcts may be a long-term sequela of ischemic insult at the time of or prior to the insertion of the renal allograft.

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Technetium-99m-dimercaptosuccinic acid (DMSA) is a radiopharmaceutical that localizes in the proximal tubular cells of the renal cortex (*1*), thus allowing visualization of functioning renal parenchyma. The major route of uptake is directly from peritubular capillaries, but some is via glomerular filtration (*2*). The role of ^{99m}Tc-DMSA studies in the detection of acute pyelonephritis (*3,4*) and in the evaluation of reflux nephropathy (*5*) is established. In the piglet model with acute urinary tract infection, the DMSA changes correspond to acute pyelonephritic foci (*6,7*). Further, the DMSA changes seen in reflux nephropathy correspond to renal scars (*8*). The use of ^{99m}Tc-DMSA studies in renal allografts has not been well assessed and it was thus decided to evaluate this group. This study documents large focal peripheral cortical abnormalities detected in renal allografts using DMSA.

MATERIALS AND METHODS

Nineteen renal cortical studies were performed in 10 male and 9 female children with renal allografts. The recipient's age at transplantation was from 1 yr and 7 mo to 18 yr and 10 mo with a mean age of 10 yr and 8 mo. Thirteen patients received cadaver kidneys and six patients received kidneys from living related donors. In 17 children, DMSA studies were performed 3 hr after intravenous injection, the dose adjusted for age with a maximum of 60 MBq. In two children, scans were performed 3 hr after intravenous injection of ^{99m}Tc-gluconate (which has similar cortical imaging properties to DMSA) using an age-adjusted dose to a maximum of 250 MBq. Anterior high-resolution parallel-hole collimated planar views and anterior pinhole images of the transplant kidney were acquired on a large field of view gamma camera (Starcam 400 AC: General Electric, Milwaukee, WI). Informed consent was obtained from the parents or guardians of all the children enrolled in this study.

The donor clinical data were reviewed and the following information obtained: age, sex, pre-harvest serum creatinine, history of hypertension, urine output, ischemia time of the graft, whether machine perfusion of the graft was undertaken for graft preservation and any peculiarities of vascular anastomoses. Recipient data gleaned included an assessment of initial graft performance using the time it took to halve the pre-transplant serum creatinine and the time to achieve a steady serum creatinine, serum creatinine at the time of the study, and age of the graft at the time of the study. Clinical data including thrombocytosis, immunosuppressive regimen, number of rejection episodes, number of post-transplantation urinary tract infections, and antihypertensive therapy requirements were recorded and correlated with the scan findings.

Statistical analysis of the influence of living related donor grafts versus cadaver grafts and double versus single renal arteries was undertaken using the Chi-squared test, whereas all other data analysis was performed using the Student's t-test.

RESULTS

The results are summarized in Table 1. Of the 19 renal allograft recipients studied, 10 were normal (Fig. 1) and 9 were abnormal (Fig. 2). In eight of the abnormal studies, multiple large focal peripheral cortical defects were found and in one allograft there was a solitary area of absent uptake in the midpole of the transplant kidney. The following clinical factors showed a positive association with abnormal allograft studies:

1. The mean ischemia time of the transplant kidney was significantly shorter in patients with normal studies than in the group with abnormal scans (9 hr

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TABLE 1
Results of Data

	Normal (n = 10)	Abnormal (n = 9)	p value
	Ischemia time 9 hr 6 min (mean) s.d. = 9 hr 24 min	22 hr 30 min (mean) s.d. = 8 hr 42 min	p = 0.003
Living related donor grafts (n = 6)	5	1	p = 0.07
Cadaver grafts (n = 13)	5	8	
Double renal arteries (n = 5)	1	4	p = 0.09
Single renal arteries (n = 14)	9	5	
Age of graft at study (mo)	14.2 (mean) s.d. = 17.1	28.0 (mean) s.d. = 27.8	p = 0.69
Donor S. creatine mmol/liter	0.095	0.088	p = 0.69
Pre-harvest urine output	156 ml/hr	191 ml/hr	p = 0.51
Time to half serum creatine	5.7 days	7.2 days	p = 0.73
Time to steady serum creatine	15.8 days	14.1 days	p = 0.83
Max cyclosporin level ng/ml	887	1168	p = 0.27
Acute rejection episodes per year of graft life	2.64	2.12	p = 0.76
Current serum creatine (mmol/liter)	0.11 (mean) s.d. = 0.042	0.11 (mean) s.d. = 0.058	p = 0.91

6 min ± 9 hr 24 min versus 22 hr 30 min ± 8 hr 42 min (mean ± s.d.) p = 0.003).

2. Cadaver grafts had more abnormal scan appearances (8 of 13 studies were abnormal) than living related donor grafts (1 of 6 was abnormal), although this just failed to reach statistical significance (p = 0.07). The only abnormal scan among the group of living related donor grafts was in the only patient in the whole study to have suffered a hyperacute rejection episode, and her DMSA study exhibited multiple large focal peripheral cortical defects. It is noteworthy that living related donor grafts suffered significantly shorter mean ischemia times when compared to cadaver grafts (1 hr 26 min versus 22 hr 56 min; $p < 0.001$). However, within the limitation of our small group numbers, it was not possible to separate statistically ischemia time and type of graft as independent variables.
3. In four of the five patients with double renal arteries, the scans were abnormal in multiple sites.

Grafts with a normal scan appearance were studied relatively earlier after transplantation than the abnormal group (14 mo versus 28 mo), though this difference failed to reach statistical significance. Analysis of all the other clinical data from donors and recipients, as described in the previous section, revealed no correlation with the scan appearances. Interestingly, grafts with a normal scan appearance showed no evidence of better initial or subsequent graft function, than grafts with an abnormal appearance.

DISCUSSION

The presence of large focal peripheral cortical abnormalities detected on ^{99m}Tc-DMSA studies performed on renal allograft recipients is an unexplained phenomenon. A possible pathophysiologic mechanism to account for these scan appearances is asymptomatic segmental graft infarction secondary to progressive vascular disease, possibly as a long-term sequela of ischemic insult at the time of, or prior to, the insertion of the renal allograft. The basis of this proposed hypothesis is the significant difference in mean ischemia time between those with normal and abnormal studies, the fact that four of five patients with double renal arteries had abnormal scans in multiple sites and that grafts with an abnormal scan appearance were studied relatively later post-transplant, suggesting that the abnormalities were due to an evolving process.

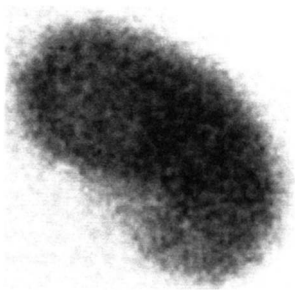

FIGURE 1. A normal ^{99m}Tc-DMSA study in a 10-yr-old child performed 8 mo after transplantation. There is uniform uptake of tracer throughout the renal cortex of the transplant kidney.

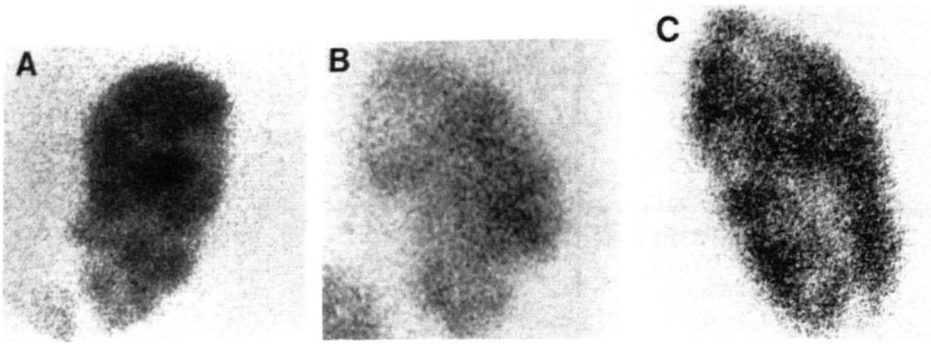

FIGURE 2. Three different examples of abnormal ^{99m}Tc-DMSA scan appearances are presented. There are multiple tical defects identified in the transplant kidneys.

Progressive vascular disease following an ischemic insult was first clearly documented in native kidneys in animal experiments published in 1959 (*9*). Sheehan and Davis demonstrated that short periods (1–2 hr) of transient total renal ischemia, followed by good reflow, resulted in the later development of gross intimal hyperplasia, presumably on the basis of vascular injury. Progressive obliterative vascular lesions in human renal allografts were first described in 1963 by Porter et al. (*10*). Biopsy data were available in 5 of our patients, who underwent 10 biopsies. The size of the defects demonstrated on the isotope studies were variable, but if their etiology was vascular, the vessels involved would have to be at least lobar arteries in size. Unfortunately no such major intrarenal arteries were seen in the biopsy specimens to allow direct correlation with the scan abnormalities, and thus the available histology was insufficient to confirm the proposed mechanism for the abnormal scan appearances.

In conclusion, the only correlates for the finding of frequent renal cortical abnormalities demonstrated by isotope studies performed on renal transplant recipients appear to be ischemia time and presence of double renal arteries. These findings are clearly worthy of a further more intensive and detailed prospective study, which we intend to undertake. We plan to compare the DMSA studies with quantitative doppler flow studies and possibly thallium scintigraphy to assess our proposed hypothesis for the scan appearances. If the abnormalities present on DMSA scan are indeed due to vascular injury, then they may have an important prognostic significance, because of the resulting loss of functioning renal cortical tissue. The fact that there is no difference in serum creatinine between the normal and abnormal groups may possibly be explained by the short mean follow-up period of approximately 2 yr.

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