Quantitative SPECT of Technetium-99m-DMSA Uptake in the Kidneys of Normal Children and in Kidneys with Vesicoureteral Reflux: Detection of Unilateral Kidney Disease

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Quantitative SPECT was used to evaluate renal functional volume (cc), percent of injected dose/cc (%ID/cc) and renal uptake (%) in 11 children with unilateral vesicoureteral reflux grade 3 or greater, and in 19 normal control children without reflux. Methods: Studies were performed 4–6 hr after intravenous injection of 0.750–2 mCi of 99mTc-DMSA. Results: Control kidneys (n = 38) had a volume of 99.7 ± 29.5 cc. The %ID/cc was 0.27 ± 0.08, and the uptake in one kidney was 24.8% ± 3.9%. Global renal uptake (right plus left) was 49.6% ± 7.3%. Functional volume of the control kidneys showed an increase with age, and the %ID/cc showed a steeper decrease with age, resulting in a trend of the kidney uptake to decrease with age. Kidneys with reflux had a decreased kidney uptake of 15.7% ± 29.5%, compared to age- and sex-matched controls (t = 4.7, p < 0.001). The contralateral kidneys without reflux had a significantly increased total uptake of 33.4% ± 6.8% as compared to controls (t = 3.44, p < 0.01). Global uptake by the kidneys was 49.2% ± 8.6% and was not statistically different from controls (t = 1.0, ns). Conclusion: Our results suggest that SPECT quantitation of 99mTc-DMSA uptake in each kidney separately could be used as a noninvasive method to assess impairment and compensation of the function of the individual kidney in children with vesicoureteral reflux.

Key Words: vesicoureteral reflux; unilateral kidney disease; technetium-99m-DMSA; SPECT


Vesicoureteral reflux (VUR) is associated with renal failure in 25% of children entering the European dialysis and transplantation program and is one of the main causes of hypertension in children and young adults (1). The damage incurred by the kidneys from VUR is seldom symmetrical, and the selection of optimal treatment and follow-up requires quantitative information about the functional status of each kidney as well as knowledge of the total renal function (2–9). The separate evaluation of the function of each kidney is therefore important in the management of such patients.

Renal function can be measured noninvasively with radionuclide studies (10–14). Several radionuclide methods have been suggested for evaluation of individual renal function, although a simple radionuclide technique has not yet been generally adopted (14). Renal cortical scintigraphy using 99mTc-labeled dimercaptosuccinic acid (DMSA) is the technique of choice in detecting renal cortical defects (15–24). The quantitation of 99mTc-DMSA uptake in each kidney separately may provide a practical index of renal function. We have developed and validated a clinically useful method for quantifying the renal uptake of 99mTc-DMSA with single-photon emission computed tomography (SPECT) in adults (10,11,25). In order to evaluate quantitative SPECT methodology for the assessment of unilateral and global renal function in a population of children with VUR, quantitative SPECT was used to measure the individual renal uptake of 99mTc-DMSA in children with vesicoureteral reflux and compared to control normal children without reflux.

MATERIAL AND METHODS

Patient Population

Technetium-99m-DMSA quantitative SPECT study of the kidneys was performed on 30 children, 22 female and 8 male, with a mean age of 59 mo (range 12–132 mo). The accrual was part of the workup of children with previous urinary tract infection. All children had normal laboratory values of serum creatinine, blood urea nitrogen and urinalysis. Thirty-eight renal units of 19 children (mean age 71 mo, range 12–132 mo) with normal ultrasound, normal excretory urography, absence of reflux on voiding cystourethrography, and who had remained free of urinary tract infection for a mean period of 20 mo (range 10–48 mo) were used
as controls. Using the international classification of VUR grades (27), 11 children (mean age 40 mo, range 16–72 mo) had unilateral VUR grade 3 or greater.

Quantitative SPECT

The technique has been previously discussed in detail (26) and will be described here briefly. Quantitative SPECT of DMSA uptake by the kidneys was measured using the same methodology as in previous studies (10,11,25). The patient was injected with 0.750–2 mCi of Tc-DMSA and SPECT was performed after 4–6 hr. The amount of radioactivity was corrected for decay from the time of preparation to the time the study was actually performed. The studies were performed using a rotating gamma camera (Elscint Apex 415-ECT, Haifa, Israel) and an all-purpose, low-energy collimator. Data acquisition lasted 20 min and required 120 projections (3 degrees apart), and the entire study accumulates 3–5 × 10^7 counts. Raw data were reconstructed by filtered back-projection with a Hanning filter with a cutoff point of 0.5 cycle/cm. Data were analyzed and stored on an Elscint SP-1 computer with an optical disk. This 32-bit computer utilizes our program (26) for quantitative SPECT calculations. After reconstruction, each image was sectioned at one-pixel (0.68 cm) intervals in the transaxial, coronal and sagittal planes using a 64 × 64 byte matrix.

Kidney volumes and radioactive concentration measurements were calculated on the reconstruction data using the threshold method. After performing a series of phantom measurements with known volumes and concentrations, a threshold value of 43% was found to be optimal for Tc-DMSA (26). It should be realized that when other equipment or other reconstruction algorithms are used, the threshold value and SPECT values of phantom concentration used for conversion of counts/voxel to μCi/cc should first be evaluated. In addition, a series of phantom measurements as previously reported should be performed.

The operator chooses the best slice to define the kidney and draw a region of interest (ROI) around the organ. For volume measurements (cc) the number of pixels in all sections multiplied by the slice thickness is summed. For concentration measurements, the threshold value was subtracted from all pixels in the ROI in all slices. All the nonzero pixels that have higher counts than the threshold value are used to calculate concentration. Counts per voxel are converted into concentration units (μCi/cc) using the regression line obtained previously by phantom measurements (26). The percentage of injected dose per cc (%ID/cc) was calculated using this value corrected for radioactivity decay. Kidney uptake is then obtained by multiplying kidney volume (cc) and %ID/cc (10). Excellent correlation has been found between actual concentration in kidney phantoms with SPECT-measured concentration (10), indicating that the method can be reliably used to measure concentration of Tc-DMSA in the kidneys.

Statistical Methods

The paired t-test was used to compare left versus right kidneys. Unpaired Student’s t-test was performed for comparison between groups after matching for age. The functional volume, %ID/cc and total uptake by the control kidneys were correlated to age using an exponential least-square function. Values are expressed by their mean ± 1 s.d. (95% confidence intervals).

RESULTS

Controls

Control kidneys (n = 38) had a volume of 99.7 ± 29.5 cc (90.3–108.9). The %ID/cc was 0.27 ± 0.08 (0.24–0.29), and the uptake in one kidney was 24.8% ± 3.9% (23.6–26.0). The global uptake by the kidneys (right plus left) was 49.6% ± 7.3% (46.1–53.1). There was no statistically significant difference between right and left kidneys concerning the volume, %ID/cc, and total uptake (Table 1). A significant correlation was found between age and functional volume (y = 67e^{0.01x}, r = 0.62, p < 0.001). A significant inverse correlation was found between age and %ID/cc (y = 0.41e^{-0.01x}, r = 0.62, p < 0.001) and between age and uptake (y = 28e^{-0.001x}, r = 0.35, p < 0.001) (Fig. 1). For this reason, 10 control children (20 kidneys) were age- and sex-matched (mean age 50 mo, range 12–70 mo) for comparison with the unilateral reflux group (Table 1).

Unilateral Reflux

Kidneys with reflux grade 3 or more had a decreased kidney uptake of 15.7% ± 8.6% (10.0–21.4) compared to controls (t = 4.7, p < 0.001). This was associated with a significantly reduced functional volume of the kidneys to 58.4 ± 28.9 cc (39.3–77.6) (t = 4.0, p < 0.001). The %ID/cc was 0.27 ± 0.11 (0.19–0.34), similar to controls (t = 1.04, ns). The contralateral kidneys without reflux had a significantly increased total uptake of 33.4% ± 6.8% (28.9–37.9) compared to controls (t = 3.44, p < 0.01), due to an increased %ID/cc of 0.43 ± 0.16 (0.33–0.54) (t = 2.8, p < 0.01). The functional volume was 82.1 ± 29.0 cc (62.8–101.3), which was similar to controls (t = 1.0, ns) (Fig. 2). Global uptake by the kidneys (kidneys with reflux plus kidneys without reflux) was 49.2%
± 9.4% (42.9–55.4) and did not differ statistically from controls (t = 1.0, ns) (Table 1).

**DISCUSSION**

There is a need for a reliable, accurate, noninvasive method for the assessment of individual kidney function in children with VUR. Routine tests of renal function, such as serum creatinine, concentration ability and hydrogen ion excretion may show normal laboratory values even when more than half of the parenchyma is nonfunctional (2,28). Bilateral ureteric catheterization for measurement of individual kidney function is the most accurate method for evaluating renal function, but is impractical in children and carries the risk of anesthesia, trauma, infection and associated discomfort (2,10,11,29).

Several radioisotopes techniques have been proposed for measurement of individual renal function (10–14). The methods for measurement of glomerular filtration rate and effective renal plasma flow from plasma clearance of 99mTc-DTPA and 131I-hippuran are quite accurate but are cumbersome and take a long time to perform. Clinical methods based on imaging alone are less accurate (14).

Renal cortical scintigraphy using 99mTc-DMSA is useful in detecting renal cortical defects (15–24). Comparative clinical studies have shown renal cortical scintigraphy using DMSA to be significantly more sensitive than excretery urography or ultrasound in the detection of renal parenchymal involvement in children with VUR, and it is considered the imaging technique of choice for the diagnosis of acute pyelonephritis (15,17,19,24). The kidney uptake of 99mTc-DMSA provides a practical index for the evaluation of cortical function. Quantitation of 99mTc-DMSA uptake by planar scintigraphy has been attempted (30). However, the need for correction for depth and background limits the usefulness and prevents widespread acceptance (31).

Measurement of radiopharmaceutical uptake by quantitative SPECT has been achieved using a threshold method (26). Phantom studies have shown a coefficient of variation for replicate studies of less than 2%, and there was no significant difference between two quantitative SPECT studies done several months apart in the same group of control patients (32).

In previous studies we showed that the individual kidney uptake of DMSA measured by SPECT is useful in separating normal from diseased kidneys (10). Also, a good correlation was found between DMSA uptake measured by quantitative SPECT and renal function measured by creatinine clearance in patients with a single kidney, validating the measurements in each kidney separately (11).

The importance of growth of the child and its relation to renal function led us to compare our parameters with age. The functional volume of the kidneys was shown to increase with age, but the %ID/cc showed a steeper decrease with age, resulting in a trend of kidney uptake to decrease with age (Fig. 1). This functional change is in agreement with the fact that in the growing child, the glomerular surface per kidney weight decreases with age and each
functional unit of the kidney has available to it the same blood supply as in adults (33).

The present study showed a significant decrease in renal uptake of $^{99m}$Tc-DMSA in kidneys with a reflux of grade 1 or greater, as compared to control kidneys of children with no reflux (Figs. 3 and 4). It also showed increased $^{99m}$Tc-DMSA uptake in the contralateral kidneys, which had no reflux and may represent compensatory hyperfunctioning of the kidney that enabled the global kidney uptake (right plus left) to remain normal.

In conclusion, the results suggest that SPECT quantitation of $^{99m}$Tc-DMSA uptake in each kidney separately could be used as a noninvasive method for the assessment of impairment and compensation of the function of the individual kidney in children with VUR.

REFERENCES

Can DMSA Detect Early Renal Injury in Children with Vesicoureteral Reflux?

Vesicoureteral reflux occurs in approximately 1%-2% of the pediatric population. These children are at increased risk for renal scarring, hypertension and, in some instances, progression to chronic renal failure if left untreated (1). Extremely poor growth of scarred kidneys has been noted in children greater than 5 yr of age (2), however, little is known about the effects of persistent vesicoureteral reflux in patients with undamaged kidneys (3).

The recently published proceedings of the International Workshop on Reflux and Pyelonephritis (4) document the ongoing and progressive nature of renal injury in children with vesicoureteral reflux. Smellie et al. (5) originally confined the risk of renal injury to children under 2 yr of age and disclosed by longitudinal studies the continued risk of covert renal scars over subsequent years and potential deleterious outcomes such as hypertension. The association between acute pyelonephritic episodes and eventual scarring has been relatively well defined in both experimental animals and clinical studies, but we may speculate that there are more subtle methods of renal injury which may account for the eventual development of renal scars (6). By the time scarring has occurred, no remedial or preventative measures can be taken, thus a sensitive test which could show evidence of renal injury early in the process of the pathogenesis would clearly be a great advance.

Gamma camera methods of renal function measurement have gained popularity because of their relative speed, simplicity and ability to estimate split renal function without the need for ureteral catheterization. These factors are particularly important in the pediatric population in whom studies which are noninvasive and associated with minimal risk and discomfort are advantageous such as in the assessment of urinary tract infection (7). Radionuclide scintigraphy has proven to be a sensitive indicator of reflux (8), while cortical agents such as technetium-labeled glucoheptonate and dimercaptosuccinic acid (99mTc-DMSA) are useful in evaluating split renal function, to distinguish between acute pyelonephritis and cystitis, and to assess changes in function and the development of scarring over time (9). Although glucoheptonate has the advantage of a lower radiation dose, retention in the renal pelvis can interfere with interpretation and cause artifacts when using SPECT imaging techniques. Because of the excellent cortical visualization obtained with 99mTc-DMSA, of which 40% is bound in the tubules, it has become the agent of choice for SPECT imaging and for quantitation of renal function. SPECT imaging obviates the need for depth correction and minimizes the effects of background activity that have limited the usefulness of planar scintigraphy in measuring renal function. Groshar et al. (10) have previously validated a method of separating normal from diseased kidneys using abolute individual kidney uptake of 99mTc-DMSA.

In this issue, Groshar et al. have provided data to support the use of 99mTc-DMSA quantitative SPECT studies as determinants of individualized kidney unit function in children with vesicoureteral reflux. In normal controls, they found a significant correlation between age and functional kidney volume as measured by 99mTc-DMSA renal uptake. Because of the inverse correlation between age and renal uptake of 99mTc-DMSA both globally and per unit volume, it is important that controls and subjects are age matched. Although kidneys associated with significant reflux had reduced functional volume, it is interesting that the percent 99mTc-DMSA uptake per unit volume was similar to that measured in controls. Contralateral normal kidneys in these subjects had significantly increased global uptake secondary to increased 99mTc-DMSA uptake per unit renal volume, which may represent compensatory hyperfunctioning.

The techniques described in this paper may well fulfill the need for more sensitive and specific indicators of early renal injury, and we would suggest that others explore this same methodology in future trials to confirm or validate these findings. These techniques could also be explored as a means of assessing early renal injury in populations other than those with reflux, such as infants with antenataly detected hydronephrosis. Some of these infants have had similarly detected global reduction in renal volume associated with vesicoureteral reflux (11). It may be that the techniques...