
Diuretic MAG3 Scintigraphy (F₀) in Acute Pyelonephritis: Regional Parenchymal Dysfunction and Comparison with DMSA

George N. Sfakianakis, Felipe Cavagnaro, Gaston Zilleruelo, Carolyn Abitbol, Brenda Montane, Mike Georgiou, Shabbir Ezuddin, William Mallin, Efrosyni Sfakianakis, and Jose Strauss

Division of Nuclear Medicine, Department of Radiology; Division of Pediatric Nephrology, Department of Pediatrics; and Department of Medicine, University of Miami School of Medicine, Miami, Florida

^{99m}Tc-DMSA late static planar imaging or SPECT is being used for the investigation of focal acute pyelonephritis (APN), especially in children with urinary tract infection (UTI). Diuretic ^{99m}Tc-mercaptoacetyltriglycine (MAG3) dynamic scintigraphy has been applied in the evaluation of kidney function and structure, frequently to exclude obstruction. However, in children and adults with a clinical picture of APN, diuretic MAG3 scintigraphy with zero time injection of furosemide (MAG3-F₀) was observed to display focal parenchymal abnormalities; regional dysfunction (focal parenchymal decrease in early uptake; slow filling in and prolonged late retention of activity); or, less frequently, fixed defects. This observation was further studied both retrospectively and prospectively, and its sensitivity and specificity for APN were compared with those of dimercaptosuccinic acid (DMSA). **Methods:** In the retrospective study, for 36 children with UTI and regional parenchymal findings on MAG3-F₀, data were reviewed, analyzed, and compared with the results of concurrent DMSA studies. In the prospective study, for 57 children with clinical and laboratory findings suggestive of APN, the 2 radiopharmaceuticals were used for imaging sequentially and the results of the 2 studies were compared. The criteria for abnormal findings compatible with the diagnosis of APN were, for MAG3-F₀, regional parenchymal dysfunction and fixed focal defects and, for DMSA, focal defects without parenchymal loss. **Results:** In all groups of patients, most abnormal MAG3-F₀ studies (80%) showed regional parenchymal dysfunction, but in some (20%) a fixed defect was found. Compared with DMSA and when both regional dysfunction and focal defects were considered, MAG3-F₀ was as sensitive as DMSA. Some patients had only MAG3-F₀ abnormalities, suggesting a slightly lower specificity for MAG3-F₀ compared with DMSA (86%); this finding needs further study, because it also raises questions about the sensitivity of DMSA, considering that only a small percentage of patients with clinically suggestive findings had abnormal study findings. In most patients with fixed defects on both DMSA and MAG3-F₀, follow-up studies showed no resolution, suggesting that a fixed defect on MAG3-F₀ may indicate either more severe APN or preexistent scars and that regional dysfunction may be a sign more specific for APN and prognostic of potential recovery. In addition, a pattern more specific for a scar—a fixed defect with a dilated regional calyx—was seen on follow-up MAG3-F₀. **Conclusion:** A

fast (25-min) planar dynamic MAG3-F₀ study was found to be as sensitive at depicting focal parenchymal abnormalities in APN as was the 3- to 4-h DMSA routine procedure. The sensitivity and specificity of both studies need further evaluation.

Key Words: acute pyelonephritis; scars; dimercaptosuccinic acid; mercaptoacetyltriglycine; furosemide renography

J Nucl Med 2000; 41:1955–1963

The clinical and laboratory classification of a urinary tract infection (UTI) as lower versus upper remains controversial in pediatrics, mainly because of the lack of classic symptomatology, particularly in early childhood, when UTIs are relatively common. In addition, laboratory tests of blood and urine have shown poor sensitivity and specificity for this task. However, it has been established that acute infections of the renal parenchyma (acute pyelonephritis, or APN) lead to scarring, which is often subsequently associated with complications such as hypertension, proteinuria, and loss of renal function; all these factors may lead to renal insufficiency and failure (1). This fact was recently reinforced by several studies in humans and in animal models showing that only those bacterial infections reaching the renal parenchyma result in cortical renal scars (2). Another observation is that the younger the patient is, the greater is the possibility of scarring (3). Finally, predisposing factors such as congenital anomalies of the urinary tract or vesicoureteral reflux are an important cause in some patients (4). In most patients, however, APN is not commonly associated with demonstrable anatomic or functional abnormalities (5). In animals, at least, early aggressive antibiotic treatment can abort the development of renal scarring (6). Also well established in patients with APN is the fact that radiography and sonography lack sensitivity whereas renal scintigraphy with ^{99m}Tc-labeled cortical fixation agents (dimercaptosuccinic acid [DMSA] or glucoheptonate) has excellent sensitivity in the diagnosis of APN (7–9). Experimental work in piglets showed DMSA imaging to be highly sensitive in detecting induced APN as focal defects (10). In addition, in children with previously normal kidneys who present with

Received Sep. 22, 1999; revision accepted May 16, 2000.

For correspondence or reprints contact: George N. Sfakianakis, MD, Division of Nuclear Medicine (D-57), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.

UTI, focal areas of decreased or interrupted function (focal defects) are highly specific for APN (11).

DMSA, a renal radiopharmaceutical localized by distal tubular fixation (40% of the dose), is considered to be the best available radiopharmaceutical for the scintigraphic evaluation of APN because of high kidney-to-background ratio, lack of activity in the collecting system, and lack of liver and bowel activity (11). After experimental work and clinical experience, DMSA imaging is considered the gold standard for the diagnosis of APN, especially in children with, usually, no previous renal abnormalities. After injection, a waiting period is required for 40% of the dose to accumulate in the renal parenchyma and for the rest to be excreted in the urine. The typical image of APN on delayed (3- to 6-h) DMSA imaging (planar imaging with a parallel-hole or pinhole collimator or SPECT) is characterized by a focal cortical defect with preservation of kidney volume. With effective therapy, the defect of the acute infection may resolve; otherwise, a scar will develop, as manifested by a focal defect accompanied by parenchymal collapse and loss of volume (11).

^{99m}Tc-MAG3 (mercaptoacetyl triglycine or mertiatide [TechneScan; Mallinckrodt, St. Louis, MO]) is predominantly a proximal tubular secretion renal agent without cortical fixation; therefore, it is not suitable for delayed imaging of the renal cortex. MAG3 is indicated for dynamic renal studies to evaluate cortical tubular function and collecting system drainage and is the agent of choice for obstructive uropathy and diffuse functional abnormalities of the renal cortex (12). However, because of high extraction efficiency (40%–60% per pass), MAG3 accumulates rapidly in the cortex during the first few minutes after injection, while the background activity is also rapidly declining. Thus, MAG3 provides images with a sufficiently high kidney-to-background ratio and acceptable resolution at 2–4 min after injection and, therefore, has been considered in the evaluation of focal parenchymal disorders (13,14). Reports about the use of MAG3 in APN are conflicting because some authors found MAG3 equivalent to DMSA (13) and others found it inferior (14). However, in those studies, MAG3 was used without the benefit of a diuretic, and investigation of the renal parenchyma focused on the first 2–3 min after injection. Experience in our laboratory shows that using a diuretic simultaneously with MAG3 (furosemide at zero time, or F₀) produces prompt diuresis, which eliminates physiologic urine activity from the calyces and renal pelvis. Thus, findings in the renal parenchyma (cortex), which occur at more than 10 min after injection, can become prominent and easily recognizable. Abnormalities in the rate of discharge of renal parenchymal activity, which appear as focal parenchymal restoration or even relative retention of activity after 10 min, may not be visible unless overhydration is present or a diuretic is injected either before or at the time of injection of MAG3.

At the University of Miami/Jackson Memorial Hospital

Nuclear Medicine Laboratories, renal scintigraphy with MAG3 has been used for evaluation of congenital and acquired renal diseases (15,16). Immediately after injection of the radiopharmaceutical, furosemide has been routinely administered to empty the normal drainage system and exclude obstruction, allow study of the renal parenchyma, and reduce radiation exposure to the urinary bladder by inducing frequent urination (17). Abnormalities in accumulation and discharge of cortical activity with MAG3-F₀ have been observed in renal parenchymal disorders, including APN (18–20). In APN, a type of regional parenchymal dysfunction has been noticed, characterized by decreased and slow or even absent early (1- to 4-min) parenchymal activity associated with late normalization or even prolonged relative retention during the later (10- to 20-min) stages of the examination (18–20).

The purpose of this article is to formalize and report the final results and conclusions of MAG3-F₀ scintigraphy as observed in APN and as compared with DMSA. The hypothesis of the prospective study was that the 2 radiopharmaceuticals and the 2 methods have comparable sensitivity and specificity in diagnosing APN. If true, then MAG3-F₀ (providing a diagnosis within 25 min) would be preferable to DMSA (requiring a wait of 3–4 h).

MATERIALS AND METHODS

The original observations were made on 60 patients with a variety of renal diseases whose MAG3-F₀ scintigraphic studies had shown some type of renal parenchymal dysfunction, diffuse or focal (Table 1) (21–23). Of these patients, 18 had a diagnosis of

TABLE 1
Patients in Whom Renal Parenchymal Dysfunction Was Observed, Prompting Retrospective and Prospective Studies

Diagnosis	Focal	Diffuse
APN	18 (unilateral or bilateral)	
Nephrotic syndromes*		14 (bilateral)
Trauma	3 (unilateral)	
RVH (before or after ACE-I)	3†	7‡ (unilateral or bilateral)
Transplants		
Acute tubular necrosis	1 (plus less intense diffuse)	6
Rejection		6
Toxicity		1
Infarcts	2	
Total	27	34

*Lupus, HIV, sickle cell disease, other.
†Branch renal artery stenosis.
‡Main renal artery stenosis.
RVH = renovascular hypertension; ACE-I = angiotensin-converting enzyme inhibitor.

APN, 17 of whom had gallium studies verifying focal infection. These observations prompted a cross-sectional retrospective study and, later, a prospective study.

Retrospective Study

A retrospective review of the records indicated that a total of 40 children with a strong clinical and laboratory suggestion of APN had abnormal MAG3-F₀ findings. These studies were performed to exclude obstruction or other congenital anomalies of the kidneys after questionable or inconclusive renal sonography findings. In 36 of 40 children (newborn to 11 y old), MAG3-F₀ studies were negative for congenital anomalies but showed focal parenchymal abnormalities (Table 2). Twenty-eight of these 36 children underwent concurrent (within 1 wk) planar DMSA studies to obtain evidence of focal APN. Many children with similar indications had normal MAG3-F₀ and DMSA findings, but the exact number could not be compiled. Follow-up (3–6 mo later) MAG3-F₀ scintigraphic studies were available for 16 of the 36 patients in this group, and 14 of the 16 also had DMSA studies (Table 2).

These studies were reviewed by 2 nuclear physicians working together in conference. When dual MAG3-F₀ and DMSA studies were available, each pair of studies was interpreted simultaneously and comparatively. When follow-up studies were available, they were reviewed in comparison with the acute studies (Table 2).

Prospective Study

The study was approved by the institutional research board, and informed consent was obtained for every patient. Five children with a documented (through urinalysis) previous history of UTI, congenital urinary tract malformations, or autoimmune disease were excluded from the study. Fifty-seven children younger than 6 y (39 boys, 18 girls; age range, 8 d to 6 y; mean age, 10.4 mo) who had fever (>37.5°C) and positive urine culture findings and were admitted to the Children's Center at the University of

Miami/Jackson Memorial Hospital during a 3-mo period participated in this study (Table 3). Eighty-four percent (48/57) were younger than 2 y, and 72% (41/57) were younger than 1 y. None of the boys were circumcised, and some infants were breast-feeding.

Each patient in whom APN was clinically suspected underwent routine blood studies (C-reactive protein, erythrocyte sedimentation rate, circulating blood counts with differentials, serum electrolytes, creatinine, and blood cultures) and urine studies (urinalysis and urine culture) during the first 24 h after admission. All patients began receiving intravenous antibiotics (cefotaxime and, in newborns, ampicillin) on admission, and their treatment was later changed according to bacterial culture and sensitivity findings. Urine culture findings were considered positive when they showed a single urinary tract pathogen in any concentration in urine obtained by suprapubic tap, greater than 10³ colony-forming units/mL if the urine was obtained by catheter, or greater than 10⁵ colony-forming units/mL if the urine was obtained by a clean and midstream catch.

When the result of the urine culture was positive (24–48 h after admission), a diuretic MAG3 dynamic renal study and renal sonography were performed. The protocol required that DMSA SPECT be performed within the next 24 h, if possible. Thus, the 2 scintigraphic tests were performed sequentially (40 within 24 h, 6 within 48 h, 4 within 72 h, and 7 within 1 wk). Finally, the imaging studies were completed with a cystogram (either nuclear or radiographic) once the repeated urine cultures were negative for pathogens. Of the 57 children included in the analysis, 6 (10.5%) had not been studied with cystography and in 3 (5.3%) the urine culture was misclassified in the laboratory (but was positive for a significant number of gram-negative rods).

Each pair of prospective studies was interpreted once simultaneously and comparatively by 2 nuclear medicine physicians working in conference and once separately and blindly by 2 other

TABLE 2
Results of Retrospective Analysis of Abnormal MAG3-F₀ Studies in Comparison with DMSA (Paired Studies) and Follow-Up Studies

Patients	MAG3-F ₀ results								Complete resolution on follow-up studies				
	2-min image		20-min image			Dilated calyx		Defect on DMSA		Reflux on cystography		Yes	No
	Defect	Hypo	Hyper*	Equal†	Defect	Yes	No	Yes	No	Yes	No		
All (n = 36)	30	6	21	8	7‡	5‡	31	—	—	9	22	6	10§
Those with paired studies (n = 28)	24	4	15	7	6	4	24	24	4	9	19	5	9

*Areas with early depressed or absent activity with delayed retention.

†Areas of early decreased or absent activity with delayed normalization.

‡Five of 7 kidneys with fixed defect were associated with dilated calyx (scars?).

§Follow-up studies were available for 16 patients. All patients without resolution had fixed defects on follow-up studies; of them, 7 had fixed defects during APN and 3 had regional parenchymal dysfunction. Seven had dilated calyces, 5 unchanged from acute phase and 2 with previous regional parenchymal dysfunction. Three patients had fixed defects without dilated calyx, 2 unchanged from acute phase and 1 with previous regional parenchymal dysfunction. It appears that fixed defects in acute phase have either worse prognosis for recovery than regional dysfunction or may represent preexistent scars.

||Of 4 patients without DMSA defects, 1 showed fixed defect on MAG, and 3 showed small area of early decreased activity, with delayed hyperactivity.

Defect = focus of no activity; hypo = focus of decreased activity; hyper = focus of increased activity; equal = activity equal to that of rest of kidney.

TABLE 3
Results of Prospective Study

MAG3 findings	DMSA SPECT findings			
	Positive	Negative	Suggestive	
Positive	15	10	5	—
Negative	33	—	32	1
Suggestive	9	2	1	6
Total	57	12	38	7

When the 2 readings disagreed, study was considered suggestive.

nuclear physicians working independently. Disagreements were categorized as suggestive (Table 3). A computer monitor with adjustable intensity was used for all DMSA and MAG3-F₀ readings.

Imaging Protocols

The standard protocol for MAG3-F₀ required hydration (oral, using 10 mL/kg water, milk, or other liquid, or intravenous) but no sedation or bladder catheterization. A 22-min (2 min per image) planar dynamic study using a computer-supported stationary or portable gamma camera with a low-energy high-sensitivity collimator was acquired in posterior projection with the patient supine, after an intravenous injection of 37–370 MBq (1–10 mCi) MAG3 and after 1 mg/kg (maximum, 40 mg) furosemide was injected immediately after the radiopharmaceutical (at time zero, F₀). A postvoiding or postupright holding image at 25 min completed the study. MAG3 studies were reviewed as 2-min sequential planar images.

Planar DMSA imaging for the retrospective study was performed 4–6 h after an intravenous injection of 19–148 MBq (0.5–4.0 mCi) ^{99m}Tc-DMSA. A pinhole collimator was used for infants, and a high-resolution parallel-hole collimator was used for older children. Posterior and oblique posterior right and left images with 150,000 and 500,000 counts per image were acquired for infants and older children, respectively. The patients were restricted without sedation in the supine (parallel-hole imaging) or prone (pinhole imaging) position. If the patient moved, the images were repeated.

DMSA SPECT (tomographic) for the prospective study was performed 3–5 h after an intravenous injection of 37–185 MBq (1–5 mCi) DMSA, using a 3-detector gamma camera with ultra-high-resolution collimators, 360°, step-and-shoot mode, 40 s, and 4° per stop. The patients were restricted without sedation. SPECT DMSA studies were reviewed as 1-cm slices in 3 projections after standard reconstruction, using a Hanning filter and a cutoff frequency of 0.2 cycles/cm.

Criteria for Interpretation

MAG3. Normal MAG3-F₀ findings were characterized by normal parenchymal and drainage function. Normal parenchyma rapidly accumulates activity and is visible with high contrast to the background at 2 min. At that time in the mature kidney (>1 mo old), the kidney-to-background ratio (kidney activity/[kidney + background activity]) is greater than 80%. Normal split renal function ranges from 45% to 55%. The contour is smooth (except for the shallow indentations around fetal lobulations), and no areas of absent or decreased activity are present, except for the limited-volume regions in the apices and over the drainage system (pelvis). Parenchymal activity peaks at 3–4 min and then declines exponentially under the influence of the diuretic, with the half-time reached before 10–12 min, and with residual parenchymal activity at 20 min less than 20% of the peak activity, smoothly distributed, and equal on both sides. Neonates have higher residual parenchymal activity (30%–40%) because their kidneys are immature. Normally, the drainage system appears at 3–5 min and its activity declines exponentially like that of the cortex. At 20 min, the drainage system may not be visible or may show slightly higher activity than does the parenchyma (Figs. 1–4, left kidney) (21).

Parenchymal dysfunction, which was observed in preliminary work (Table 1) and was the basis for inclusion in the retrospective study, was characterized by relatively decreased or even absent (focal defect) early (2 min) uptake and slowed tubular transport (10–20 min), with resultant delayed normalization or even relative retention of MAG3. Frequently, contrast enhancement was necessary to make the lesion visible, because by 15–20 min after injection, the otherwise normally functioning kidney had shed most of the activity. The parenchymal renogram showed a delay in peak time (>5 min), a flat pattern with a half-time greater than 12 min, and a residual parenchymal activity greater than 20% in the mature kidney; uptake at 2 min was reduced (kidney-to-background

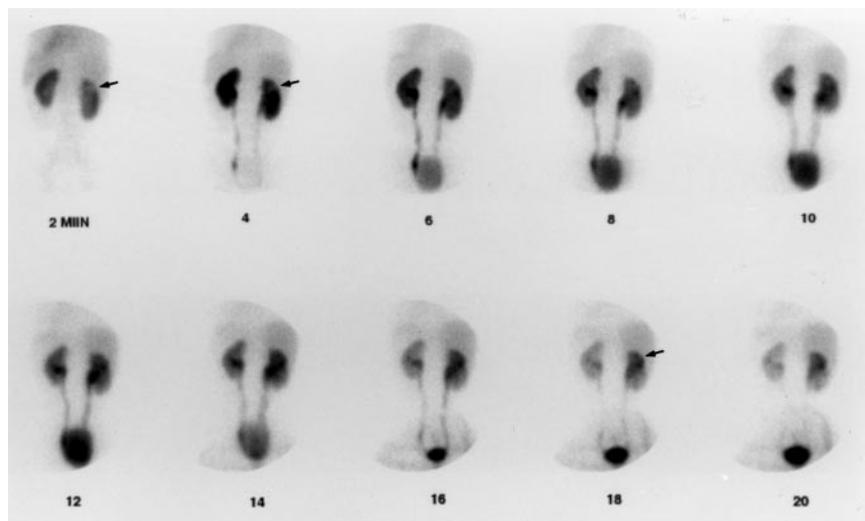


FIGURE 1. Regional parenchymal dysfunction shown on dynamic MAG3-F₀ study of child with clinical and laboratory presentation compatible with APN. At 2 and 4 min, focal parenchymal defect in right upper pole is visible (arrows). As study progresses, same area fills and eventually shows relative hyperactivity (18 and 20 min, arrow). Bladder emptied at 14 min.

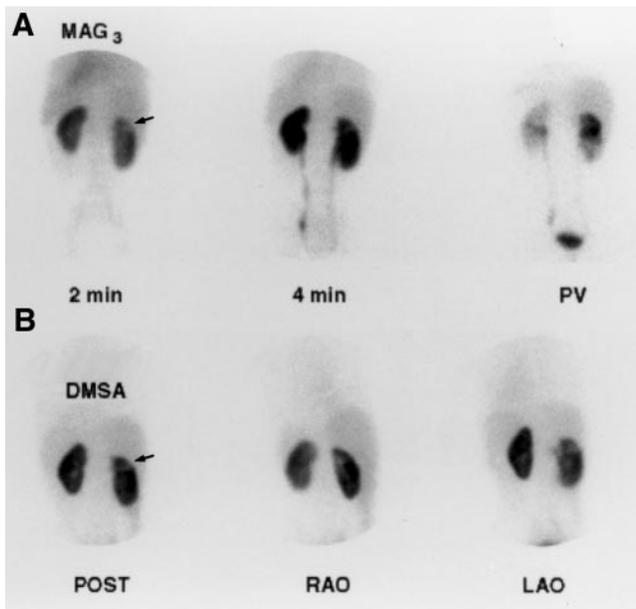


FIGURE 2. Comparison between dynamic MAG3-F₀ and static delayed planar DMSA studies obtained within 24 h in same patient as in Figure 1 shows that regional parenchymal dysfunction is compatible with APN. Focal defect without parenchymal loss (APN) by DMSA (arrow, B) coincided with regional parenchymal dysfunction by MAG3 (arrow, A).

ratio < 80%). The abnormality was transient and either focal (regional parenchymal dysfunction), involving 1 or both kidneys with 1 or more foci of abnormality present (Figs. 1–4), or diffuse (diffuse parenchymal dysfunction), involving 1 or both kidneys and the entire parenchyma (21). The renograms were abnormal focally or throughout the entire parenchyma. In some patients, a diffuse parenchymal dysfunction was present and, in addition, focal areas with more prominent retention or fixed focal defects were distinguished on the cortex (Figs. 5 and 6). Multifocal lesions were the result of either APN (Figs. 5 and 6) or other disease (Table 1).

When the scintigrams of the retrospective or prospective studies were interpreted, 2 types of focal abnormalities on MAG3-F₀ were described: regional parenchymal dysfunction with a homogeneous (Figs. 1, 2, 5, and 6) or heterogeneous (Fig. 4) pattern considered

compatible with APN, and a fixed focal defect, which was an area in which activity was persistently lacking or decreased throughout the study. A fixed focal defect was considered suggestive of APN when found in the acute phase in the prospective study. In some instances, a focal defect was bordered by regional dysfunction (Fig. 4). Such a focal defect was often associated with a prominent (dilated) calyx both in the acute phase and during follow-up of APN patients (Fig. 3). Focal defects with or without a dilated calyx were considered typical of scars when found on follow-up studies of patients with a history of APN (Figs. 3 and 4).

DMSA, Planar or SPECT. Normal findings were equally sized kidneys with 45%–55% relative (split) function and showing a smooth outline without focal defects. A focal defect, or area showing a pronounced decrease or lack of activity, was considered compatible with APN in the acute phase (Fig. 2). A focal defect, regardless of whether it was associated with perceptible parenchymal loss, was considered to indicate a scar in follow-up studies.

Statistical analysis with a paired Student *t* test was performed for the prospective study, using DMSA results as the gold standard.

RESULTS

Retrospective Study

Of 36 patients with clinical APN and focal abnormalities on MAG3-F₀, 29 showed regional parenchymal dysfunction and 7 showed fixed defects (5 with a dilated calyx). Of the 28 patients with focal abnormalities on MAG3-F₀ and paired DMSA studies, 24 showed congruent findings on both studies and 4 showed normal DMSA findings (Table 2).

Five patients had lesions bilaterally but, for the purpose of this study, were considered once. One third (9/31) of the patients were shown to have vesicoureteral reflux by nuclear or radiographic retrograde studies.

Follow-up MAG3-F₀ scintigraphy was available for 16 patients (14 with paired DMSA studies). Regional parenchymal dysfunction completely resolved in 6 patients (5 in the paired studies); it was replaced by a smaller fixed defect (associated with the development of scars by DMSA) in 3 patients (Fig. 3). In 7 patients, who originally showed fixed defects (5 with dilated calyces in the vicinity of a defect), no change in the image on follow-up scintigraphy was found. In

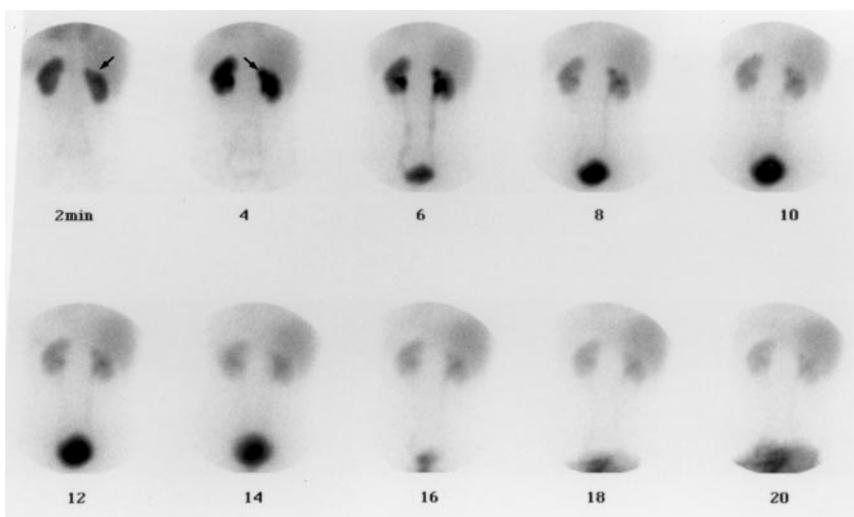
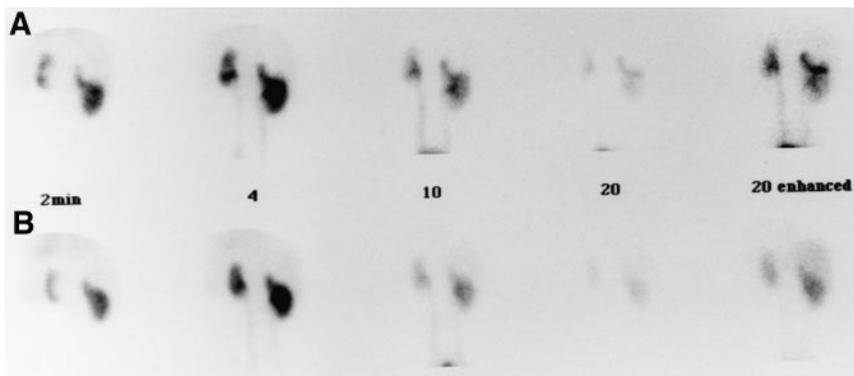


FIGURE 3. Parenchymal scar on dynamic MAG3-F₀ study in same patient as in Figures 1 and 2, performed 3 mo later, after treatment for APN. At 2 and 4 min, small focal defect with parenchymal loss is present in upper pole of right kidney (arrow). At 4 and 6 min, hyperactive (dilated) calyx is visible (arrow), but parenchymal retention does not occur later in study. This picture is compatible with small scar and is supported by concurrent DMSA study that showed small defect with parenchymal loss in same area as defect of MAG3-F₀.

FIGURE 4. APN as regional dysfunction bordering focal defect on MAG3-F₀ study. Selected images from acute (A) and 6-mo follow-up (B) MAG3-F₀ dynamic studies in same patient. Whereas dysfunctional region present on upper row appeared to have recovered in follow-up study, focal defect persisted. Such cases may indicate more severe disease, although reinfection around preexistent scar may be another possibility.



2 of the 3 patients with regional parenchymal dysfunction and fixed defects (scars), a neighboring dilated calyx was perceived in the follow-up studies.

In this as in other groups, we found that regional parenchymal dysfunction may be superimposed on diffuse dysfunction and may involve more than 1 focus of a kidney (Fig. 5). On further investigation, we observed that both the diffuse and the focal type of parenchymal dysfunction may be associated with gallium accumulation (Fig. 6). Finally, parenchymal dysfunction was occasionally bilateral and multifocal, as diffuse disease with multifocal enhancement. Such a picture could not be definitely related to APN.

Prospective Study

Scintigraphic Findings. Comparative simultaneous interpretation of the MAG3 and DMSA studies by the 2 readers working in conference showed that all but 1 of the 14 lesions

considered compatible with APN on SPECT DMSA (focal cortical defects without parenchymal loss) were visualized on the dynamic MAG3-F₀ study. They were seen either as regional dysfunction or, less frequently, as fixed focal defects. The discordant case with a defect on DMSA showed retention within the drainage system with MAG3 (probably because of vesicoureteral reflux), obliterating the delayed images of the cortex. Studies with negative findings also showed good correlation. However, in 5 patients, MAG3 findings were not associated with focal lesions on DMSA. In addition, several studies had questionable results.

The results of the masked independent interpretation by the 2 other readers working separately showed MAG3 in agreement with DMSA for 48 patients (10 positive, 32 negative, 6 suggestive), whereas in 9 patients the 2 studies were found to have different results (Table 3). MAG3 findings were positive in 5 patients with negative DMSA findings, but in no patients were the findings positive for DMSA and negative for MAG3. In 2 patients, findings were

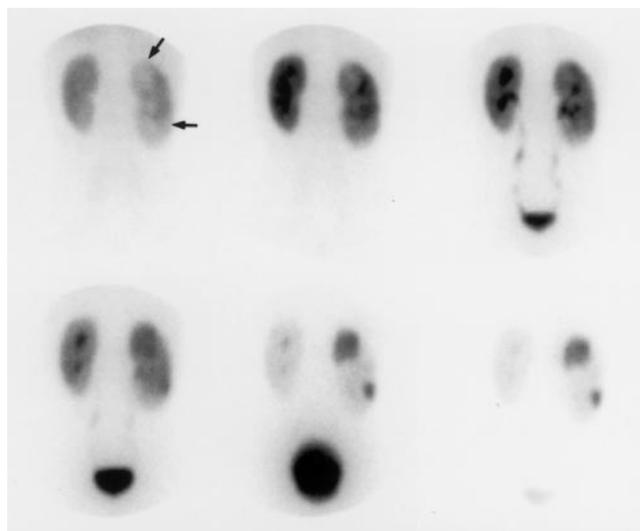


FIGURE 5. APN superimposed on kidneys with diffuse parenchymal disease. Selected images from MAG3-F₀ dynamic study in child with sickle cell disease and APN (2-, 4-, 6-, 10-, and 20-min images and 25-min image after voiding). Both kidneys are enlarged (sickle cell disease), but right kidney is edematous with decreased activity in upper and lower poles (arrows). By end of study and in 25-min image, foci of hyperactivity are present in same areas with early decreased uptake. This study, in addition to 2 foci of regional parenchymal dysfunction (APN), also showed diffuse parenchymal dysfunction caused by sickle cell disease.

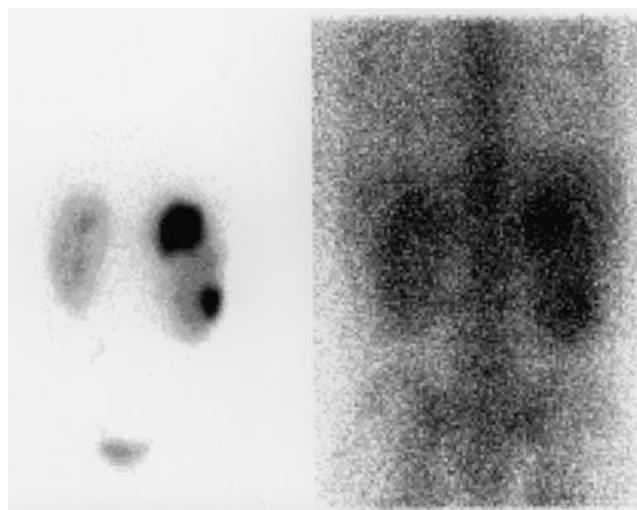


FIGURE 6. Comparison between MAG3-F₀ dynamic study (25-min image after voiding) and 48 h ⁶⁷Ga image for patient of Figure 5. Because of sickle cell disease, diffuse retention of gallium by renal parenchyma and diffuse parenchymal dysfunction are shown by MAG3. In addition, areas of APN (regional parenchymal dysfunction, as revealed by MAG3-F₀) have more intense gallium uptake than rest of kidneys.

positive for DMSA and suggestive of MAG3; in 1 patient (the patient with drainage system retention), the findings were suggestive of DMSA and negative for MAG3; and in 1 patient, the findings were suggestive of MAG3 and negative for DMSA. The MAG3-F₀ results were not statistically different from the DMSA results for sensitivity. Specificity, when DMSA was used as the gold standard for APN, was statistically different ($P < 0.05$), being somewhat reduced for MAG3-F₀ (86%).

Patient motion and the 3- to 4-h wait were problems for DMSA. Axis variations, coexistent obstruction or reflux, and lower kidney-to-background counts created difficulties with interpreting MAG3. Cortical irregularities of infantile kidneys were difficult to recognize on both studies.

Other Findings. Fever, vomiting, irritability or lethargy, and decreased appetite were the most common symptoms and signs observed in these patients. The mean rectal temperature recorded before admission was 37.9°C, with a range from 37.5°C to 41.1°C.

Urine cultures for 44 of 57 patients (77%) were positive for *Escherichia coli* (50% resistant to ampicillin); the second most common organism was *Enterococcus faecalis*, which was found in 3 of 57 patients (5%). However, no typification was performed for identification of uropathogenic strains. C-reactive protein was elevated in most patients in whom APN was shown by scintigraphy but also in many patients with negative imaging findings.

The voiding cystourethrogram or the nuclear cystogram was positive for vesicoureteral reflux in 15 of 52 patients (29%). Renal sonograms interpreted by pediatric radiologists with appropriate clinical information were not diagnostic of APN in any patient; in only 2 patients were findings suggestive of urinary infection reported because of debris in the bladder.

Hospital admissions for UTI were frequent in preschool children and even more so in infants. A high incidence of renal involvement was found by scintigraphy in febrile infants and children, confirming data previously published by various investigators (24,25). However, evidence of APN was not found or suggested by either MAG3 or DMSA in the majority (32/57) of patients admitted and originally treated for APN. The febrile episode was finally attributed to lower UTI and treated as such, although some patients with a severe clinical picture were treated for APN.

DISCUSSION

This study showed that MAG3-F₀ dynamic imaging has the same sensitivity as DMSA late scintigraphy for kidney lesions compatible with APN in children with no previous renal abnormalities. MAG3-F₀ studies were found to be slightly less specific than DMSA when the latter was considered the gold standard, but the difference was small. This experience supports the possibility that MAG3-F₀ scintigraphy may be a fast and accurate technique for the diagnosis of APN in children with the appropriate clinical and laboratory presentation.

Regional parenchymal dysfunction appeared to be a characteristic, and potentially reversible, finding for APN on MAG3-F₀ in all groups of patients studied (Figs. 1, 2, and 4–6). In addition, a fixed defect associated with the early (3- to 5-min) appearance of a hyperactive (dilated) calyx has been observed on MAG3-F₀ in scars (Fig. 3). In DMSA studies, parenchymal loss indicates that a defect is caused by a scar. Evidence suggested that a fixed focal cortical defect on MAG3-F₀ as well as on DMSA may not necessarily characterize APN and may indicate a preexistent scar.

Regional parenchymal dysfunction was usually peripheral (Fig. 5) but, in some cases, extended deeper (Figs. 1 and 4), indicating that the dysfunction may be a cortical abnormality involving the medulla as well. No drainage system abnormality was evident. In some patients, a peripheral focal defect was bordered centrally by regional parenchymal dysfunction (Fig. 4). Because MAG3 is primarily a tubular agent, the abnormality may be caused by some reversible derangement in the function of the proximal tubular cells. Although the early decrease seen in MAG3 uptake may have resulted from focal ischemia, the late retention of activity locally suggests that the abnormality is, at least in part, a tubular dysfunction. As is the case with some defects observed using DMSA, this dysfunction seen on MAG3-F₀ may resolve completely or lead to a permanent focal defect, or scar. Figure 7 illustrates a possible sequence of events (APN either resolving or leading to scar formation) based on these observations. Abnormalities found on MAG3-F₀ are nonspecific for APN (Table 1), as is the focal defect of the DMSA study.

In some patients, the clinical presentation was, on the basis of history, compatible with APN, and DMSA showed focal defects without appreciable parenchymal loss, but MAG3-F₀ did not show typical regional dysfunction. Rather, focal defects and, in some, a combination of focal defects with regional dysfunction were visible. Hence, the conclusion is that APN may be manifested on MAG3-F₀ either as regional dysfunction or as a fixed defect. However, one cannot exclude the possibility that, in some patients, unknown preexistent scars may have been the cause of focal defects on both studies. The fact that fixed defects on MAG3-F₀ did not recover function may indicate that either more severe disease or already established scars were present (Table 2). This observation, which raised doubts about the specificity (for APN) of a focal defect on DMSA or MAG3-F₀ scintigraphy, was made only after the completion of the study and, therefore, could not have been pursued prospectively. Infection-specific studies (⁶⁷Ga or labeled white blood cell imaging) in patients with renal parenchymal defects on MAG3-F₀ or DMSA may be helpful for proving the existence of APN if a preexistent scar is clinically suspected.

In the absence of renal insufficiency, lesions were well recognized on both MAG3 and DMSA, although the target-to-nontarget ratio was higher for DMSA (17). Contrast enhancement was necessary for many cases of MAG3,

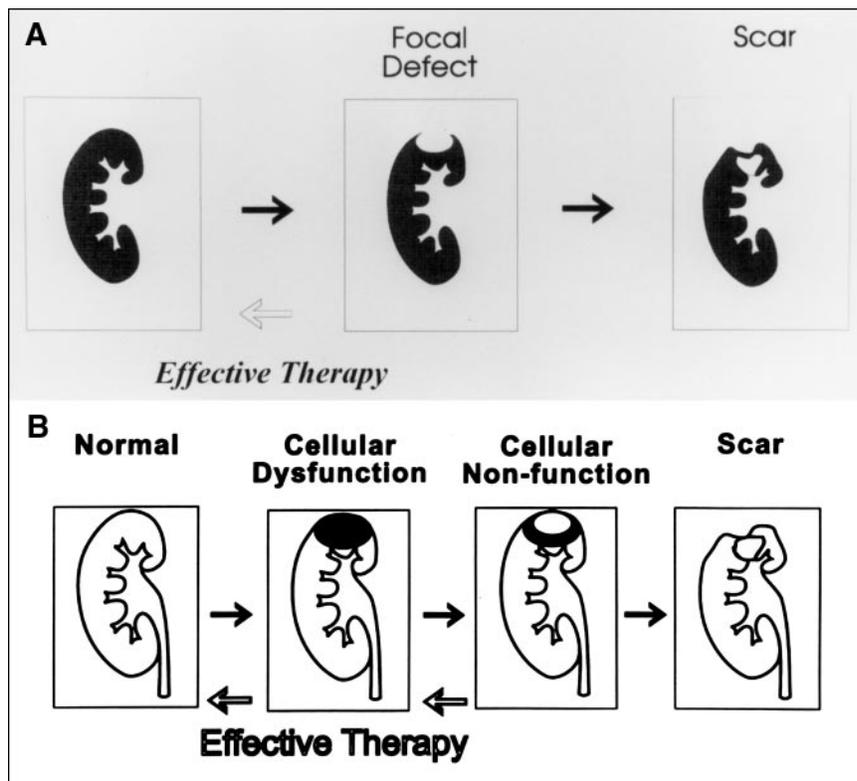


FIGURE 7. Schematic representation of findings for APN. (A) Focal defect on DMSA delayed (3- to 4-h) static images and its evolution. (B) Regional parenchymal dysfunction on MAG3-F₀ dynamic 20-min images and its evolution. Focal parenchymal area of absence or decreased activity at 2 min on MAG3-F₀ (not shown) may be associated with any of the 4 images at 20 min (B). It is suggested that, as severity of infection increases, normal 20-min image deteriorates toward focal retention and defect.

because by 15–20 min most of the activity had been shed by the kidneys. The nonscintigraphic findings in the prospective study regarding the age of the patients, the clinical presentation, the laboratory evaluation, and the contribution of retrograde studies and renal sonography to the diagnosis of APN agreed with previous studies (7–9,11).

The retrospective study was based on a biased population composed of patients with a clinical suggestion of APN, in whom MAG3-F₀ studies showed focal parenchymal findings but excluded obstruction or other congenital anomalies. No accurate data from patients without focal parenchymal findings were available for comparison. However, when both MAG3-F₀ and DMSA studies were performed, good correlation was found for identifying focal abnormalities compatible with APN.

The prospective study was needed so that tests with negative findings could be included for the evaluation of specificity. Thus, more reliable information was provided, indicating a similarity in the findings of the 2 tests, with sensitivities not statistically different. For parenchymal lesions, the findings indicated a slightly lower specificity for MAG3-F₀ than for DMSA, which is considered the gold standard for APN (10,11). This lower specificity may indicate a disadvantage of MAG3-F₀ or an overreading by the reviewers but needs to be further considered because of the questions that are raised about the sensitivity of DMSA. Because DMSA imaging is the most sensitive modality available, it was used to compare the findings of MAG3-F₀ in APN. However, experimental work on animals with no previous renal abnormalities supporting the sensitivity and

specificity of DMSA findings has indicated that not all foci of APN found on pathologic examination were associated with defects on DMSA imaging (10). In addition, the sensitivity of DMSA in detecting APN in children is better than that of any other test yet was never proved to be 100%; therefore, obtaining positive MAG3-F₀ findings with corresponding negative DMSA findings does not prove that the former were false-positive.

Finally, both methods need to address some technical difficulties, such as the cortical irregularities of infantile kidneys, axis variations, and patient positioning and motion. Also, the masked analysis indicated that imaging with either MAG3 or DMSA carries a significant risk (20% in this study) of uncertain, or suggestive, studies, as other investigators have recently also suggested for DMSA (26). Of special interest is the fact that most of the children admitted and originally treated for APN either had no evidence of focal renal abnormalities by either DMSA or MAG3-F₀ or showed positive findings on MAG3-F₀ only, raising the issue of sensitivity for both studies despite their being the most sensitive imaging tests. The small size of the kidneys in most patients is a critical issue for resolution, although motion and attenuation limitations also play a role. A higher dose of MAG3, high-resolution collimation, and combined use with tomography (SPECT MAG3) at 1–3 min after injection may further improve MAG3-F₀ results (17).

Our findings differ from those of an earlier study (14), possibly because the investigators did not use furosemide and did not recognize regional parenchymal dysfunction.

CONCLUSION

Retrospective and prospective comparative studies indicated that MAG3-F₀, by revealing regional parenchymal dysfunction or fixed focal defects, is as sensitive as planar or SPECT DMSA for APN, with the advantage of providing results within 25 min rather than 3–4 h. Further work is needed to define the relative merits of the focal defect compared with regional dysfunction in clinical settings of APN. High-resolution collimation and a higher dose of MAG3 may further improve the results. SPECT MAG3 studies acquired during the first 4 min after injection, followed by planar or SPECT imaging at 20 min, is an attractive possibility for obtaining 3-dimensional information.

REFERENCES

1. Jacobson SH, Eklof O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uremia after pyelonephritis in childhood: 27 year follow up. *Br Med J*. 1989;299:703–706.
2. Jakocsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Arch Dis Child*. 1994;70:111–115.
3. Benador D, Benador N, Slosman D, Mermillod B, Girardin E. Are younger children at highest risk of renal sequelae after pyelonephritis? *Lancet*. 1997;349:17–19.
4. Rushton HG, Majd M, Jantusch B, Wiedermann BL, Belman AB. Renal scarring following reflux and non-reflux pyelonephritis in children: evaluation with 99m-Tc-dimercaptosuccinic acid scintigraphy. *J Urol*. 1992;147:1327–1332.
5. Benador D, Benador N, Slosman DO, Nussle D, Mermillod B, Girardin E. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. *J Pediatr*. 1994;124:17–20.
6. Ransley PG, Risdon RA. Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritic scar. *Kidney Int*. 1981;20:733–736.
7. Handmaker H, Young B, Lowenstein J. Clinical experience with Tc-99m-DMSA (dimercaptosuccinic acid): a new renal imaging agent. *J Nucl Med*. 1975;16:28–32.
8. Traisman FS, Conway JJ, Traisman HS, et al. The localization of urinary tract infection with Tc-99m-glucoheptonate scintigraphy. *Pediatr Radiol*. 1986;16:403–406.
9. Sty JR, Wells RG, Schroeder BA, Starshak RJ. Diagnostic imaging in pediatric renal inflammatory disease. *JAMA*. 1986;256:895–899.
10. Rushton HG, Majd M, Chandra R, Yim D. Evaluation of 99m-Tc-dimercaptosuccinic acid renal scan in experimental acute pyelonephritis in piglets. *J Urol*. 1988;140:1169–1174.
11. Majd M, Rushton HG. Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. *Semin Nucl Med*. 1992;22:98–111.
12. Taylor A, Eshima D, Frizberg AR, et al. Comparison of I-131-OIH and Tc-99m-MAG₃ renal imaging in volunteers. *J Nucl Med*. 1986;27:793–803.
13. Gordon I, Anderson PI, Lythgoe MF, Orton M. Can technetium-99m-mercaptoacetyl-triglycine replace technetium-99m-dimercaptosuccinic acid in the exclusion of a focal renal defect? *J Nucl Med*. 1992;33:2090–2093.
14. Piepsz A, Pintelon H, Verboven M, Keuppens F, Jacobs A. Replacing 99m-Tc-DMSA for renal imaging. *Nucl Med Commun*. 1992;13:494–496.
15. Sfakianakis GN. Nuclear medicine in congenital urinary tract anomalies. In: Freeman L, ed. *Nuclear Medicine Annual*. New York, NY: Raven Press; 1991:129–192.
16. Sfakianakis GN, Vonorta K, Zilleruelo G, Jaffe D, Georgiou M. Scintigraphy in acquired renal disorders. In: Freeman L, ed. *Nuclear Medicine Annual*. New York, NY: Raven Press; 1992:157–224.
17. Sfakianakis GN, Georgiou MF. MAG₃ SPECT: a rapid procedure to evaluate the renal parenchyma. *J Nucl Med*. 1997;38:478–483.
18. Sfakianakis GN, Jacobs W, Aboud A, et al. Focal renal parenchymal abnormalities (regional dysfunction) on MAG₃ high resolution computer enhanced renal parenchymal imaging and their clinical significance [abstract]. *J Nucl Med*. 1993;34(suppl):137P.
19. Sfakianakis GN, Aboud A, Cavagnaro F, et al. The role of dynamic MAG₃ scintigraphy in the diagnosis of acute pyelonephritis: a comparison with DMSA [abstract]. *J Nucl Med*. 1993;34(suppl):117P.
20. Sfakianakis GN, Zilleruelo G, Cavagnaro F, et al. A prospective comparative DMSA and MAG₃ study in acute pyelonephritis. In: Taylor A, Nally JV, Thomsen H, eds. *Radionuclides in Nephrourology*. Reston, VA: Society of Nuclear Medicine; 1997:182–184.
21. Sfakianakis GN, Carmona AJ, Sharma A, et al. Diuretic MAG₃ scintigraphy in children with HIV nephropathy: diffuse parenchymal dysfunction. *J Nucl Med*. 2000;41:1037–1042.
22. Sfakianakis GN, Bourgoignie JJ, Georgiou M, Guerra JJ. Diagnosis of renovascular hypertension with ACE-inhibition scintigraphy. *Radiol Clin North Am*. 1993;31:8341–8348.
23. Chandar JJ, Sfakianakis GN, Zilleruelo GE, et al. ACE-inhibition scintigraphy in the management of hypertension in children. *Pediatr Nephrol*. 1999;13:493–500.
24. Conway JJ, Cohn RA. Evolving role of nuclear medicine for the diagnosis and management of urinary tract infection. *J Pediatr*. 1994;124:87–90.
25. Stokland E, Hellstrom M, Jacobsson B, et al. Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. *J Pediatr*. 1996;129:815–820.
26. Piepsz A, Blaufox MD, Gordon I, et al. Consensus on renal cortical scintigraphy in children with urinary tract infection. *Semin Nucl Med*. 1999;29:160–174.