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# Diuretic MAG3 Scintirenography in Children with HIV Nephropathy: Diffuse Parenchymal Dysfunction

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HIV nephropathy (HIVN) is prevalent in 15%–56% of HIV-infected children and induces mild to severe progressive nephropathy. **Methods:** A total of 33 renal diuretic scintirenographic studies with  $^{99m}\text{Tc}$ -mercaptoacetyltriglycine (MAG3) were reviewed and analyzed from 23 HIV pediatric patients, 21 of whom had HIVN with varying degrees of renal impairment. Results were compared with 10 studies of control patients of matching ages. Visual interpretation of images and renograms as well as semiquantitative analyses were performed. Variables compared were size of kidneys, time of peak and one-half peak activities, residual (or retained) cortical activity at 20 min, ratio of cortical activity at 2.5–20 min, and ratio of kidney activity to kidney plus background activity at 2 min. The results of MAG3 renal studies were also compared with laboratory data pertaining to creatinine clearance in all patients and with sonography in 17 patients. **Results:** In most patients with HIVN (18/21), the kidneys were larger than normal, with a diffuse parenchymal dysfunction (decreased uptake, slow processing, and increased retention of activity) and flat renograms, findings similar to those observed in other diffuse parenchymal diseases. In all patients with HIVN, semiquantitative analysis (paired *t* test) showed statistically significant differences from control patients for all variables. On ANOVA, a statistically significant correlation was found between most scintigraphic parameters and the severity of renal impairment. Of the 17 concurrent sonographic studies in HIVN patients, 7 showed no abnormalities, whereas the results of scintigraphy were abnormal. **Conclusion:** Diuretic MAG3 scintirenography shows nonspecific diffuse parenchymal dysfunction in pediatric patients with HIVN. Such dysfunction may provide corroborative evidence of HIVN and should be recognized when the test is performed for standard indications. Further work is necessary to prove that the test has indeed the high sensitivity and good correlation with the severity of HIVN suggested in this population; the test may be useful to follow up the progression of disease and the effect of treatment.

**Key Words:**  $^{99m}\text{Tc}$ -mercaptoacetyltriglycine; HIV nephropathy; pediatrics; scintirenography; AIDS

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In 15%–56% of HIV-infected children with or without AIDS, HIV nephropathy (HIVN) develops (1). HIVN is one of many types of renal parenchymal involvement in HIV-infected patients. Acute tubular dysfunction, renal failure caused by other infections or nephrotoxic drugs, hemolytic uremic syndrome, thrombocytopenic thrombotic microangiopathy, multiorgan failure, glomerulopathy related to immunologic abnormalities, and HIVN may be found in HIV-infected patients (2). HIVN is defined as significant persistent proteinuria (>1+ by dipstick, or a urinary protein-to-creatinine ratio > 0.2) in HIV-infected patients on at least 2 occasions, without any other demonstrable cause and without radiologic findings consistent with other renal diseases (3). The cause of HIVN is unclear; direct infection by the HIV virus, coinfection by another virus, apoptosis, cytokines, ischemia, and host-directed viral immune-mediated injury are likely mechanisms (3). No single morphologic feature is specific for HIVN, and the glomerular changes range from a minimal change to mesangial hyperplasia to focal segmental glomerulosclerosis (4–8).

The glomerular changes and microcystic dilatation of the tubules manifest as nephromegaly and increased echogenicity on the sonographic examination. Sonography has been used in clinical practice to examine HIV patients for HIVN. Enlargement of the kidney, loss of corticomedullary differentiation, and increased echogenicity constitute findings supporting the diagnosis of HIVN. The sensitivity of this noninvasive and easily applied modality is not firmly established, and no definite correlation has been found between the sonographic findings and the degree of renal impairment (9,10).

Limited information is available in the literature about radionuclide studies in HIVN, and, to our knowledge, nothing specific is available about mercaptoacetyltriglycine (MAG3). However, MAG3 has been proposed as an agent suitable for functional studies (11). The purpose of this article is to report findings on MAG3 renal scintigraphy and renography observed in children with HIVN.

## MATERIALS AND METHODS

From January 1991 to January 1997, 33 scintigraphic studies were performed on 23 pediatric patients (age range, 10 d to 19 y;

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mean age, 5.4 y) with proven HIV infection using the predominantly tubular agent  $^{99m}\text{Tc}$ -MAG3 ( $^{99m}\text{Tc}$ -meritide or TechnoScan MAG3; Mallinckrodt, St. Louis, MO). Of the 23 patients, 21 had well-documented HIVN at the time of the MAG3 study, and HIVN developed later in 2. Seven patients had follow-up studies (4 had 2 studies and 3 had 3 studies). None of the 23 patients had other congenital or acquired renal abnormalities found by clinical or laboratory evaluation, sonography, or scintigraphy. They underwent MAG3 scintigraphy as part of a prospective study to evaluate HIV patients for HIVN, approved by the institutional review board. Informed consent was obtained from the patients, the parents, or guardians. The study population included patients infected with HIV as defined by positive serology findings. HIVN was defined as significant persistent proteinuria greater than 1+ or a urinary protein-to-creatinine ratio of more than 0.2 in HIV-infected patients on at least 2 occasions, without fever or any other demonstrable cause or any clinicopathologic or radiologic findings consistent with renal disease.

MAG3 renal studies from 10 patients who were being examined to exclude acute pyelonephritis or scars were selected as controls and analyzed. The patients were not HIV positive, and clinical, laboratory, and imaging methods had shown them to be free of congenital or acquired renal disorders. They were of similar ages to our HIV patients (1 control patient for each pair of HIV patients of approximately the same age).

The studies were acquired with a  $\gamma$  camera having a large field of view and a general-purpose collimator in a supine posterior projection. The patients were not sedated, but their motion was restricted. They were hydrated with water beginning 30 min before the initiation of the study (10 mL/kg orally or with intravenous fluids as clinically indicated). MAG3 in a dose of 37–370 MBq (1–10 mCi) was injected intravenously. To promptly empty the intrarenal drainage system and allow evaluation of the renal parenchyma, we administered an intravenous diuretic (furosemide, 1 mg/kg; maximum, 40 mg) immediately after injection of the radiopharmaceutical. The study was recorded as 30-s frames for 22 min. Flow studies were not used.

After acquisition, the 30-s frames were used to generate renograms and were also grouped in 2-min sequential images for visual interpretation. Standard renograms of the renal cortices were generated, and semiquantitative variables were obtained for the relative size of the kidneys (width of kidney/width of abdomen), the peak time of the renograms (Tp), the time to one-half peak activity (T 1/2), residual (or retained) cortical activity (RCA, activity at 20 min  $\times$  100/peak activity), original cortical activity (OCA, activity at 2.5 min/activity at 20 min), and kidney uptake at 60–120 s after injection (KU, ratio of kidney activity to kidney + background activity). As part of the routine protocol, the differential kidney function (split renal function) was calculated from the activity in the 1- to 2-min images with background correction.

All patients ( $n = 23$ ) underwent physical examination and analysis of creatinine clearance (CrCl, in mL/min/1.73 m<sup>2</sup> calculated using the height index formula of Schwartz et al. (12)), urine, and blood chemistry. The patients with HIVN ( $n = 21$ ) were distributed into 3 groups according to the degree of renal impairment as reflected by CrCl: group 1 ( $n = 10$ ), patients with normal CrCl to mild renal impairment (CrCl = 50–100 mL/min/1.73 m<sup>2</sup>); group 2 ( $n = 5$ ), patients with moderate renal impairment (CrCl = 25–50 mL/min/1.73 m<sup>2</sup>); and group 3 ( $n = 6$ ), patients with severe renal impairment (CrCl < 25 mL/min/1.73 m<sup>2</sup>).

Two nuclear medicine specialists, with experience in reading

pediatric cases and knowledge of the indication, visually interpreted the scintigrams and renograms in conference. The criteria for interpretation were the intensity of the activity in the kidneys compared with the background at 2 min (uptake), the progression of activity, and the discharge of activity from the renal parenchyma during the study (at 10–20 min), with emphasis on the 20-min image (Fig. 1A); the size of the kidneys compared with the size of the body, based on the subjective impression of the reviewers; and the pattern of the cortical renograms (Fig. 1B).

Semiquantitative results from the MAG3 studies of patients with HIVN were first compared as a whole with the control studies (Table 1; Fig. 2). Subsequently, the indices were compared among the 3 groups and correlated with the severity of renal impairment by CrCl (Table 2; Fig. 3).

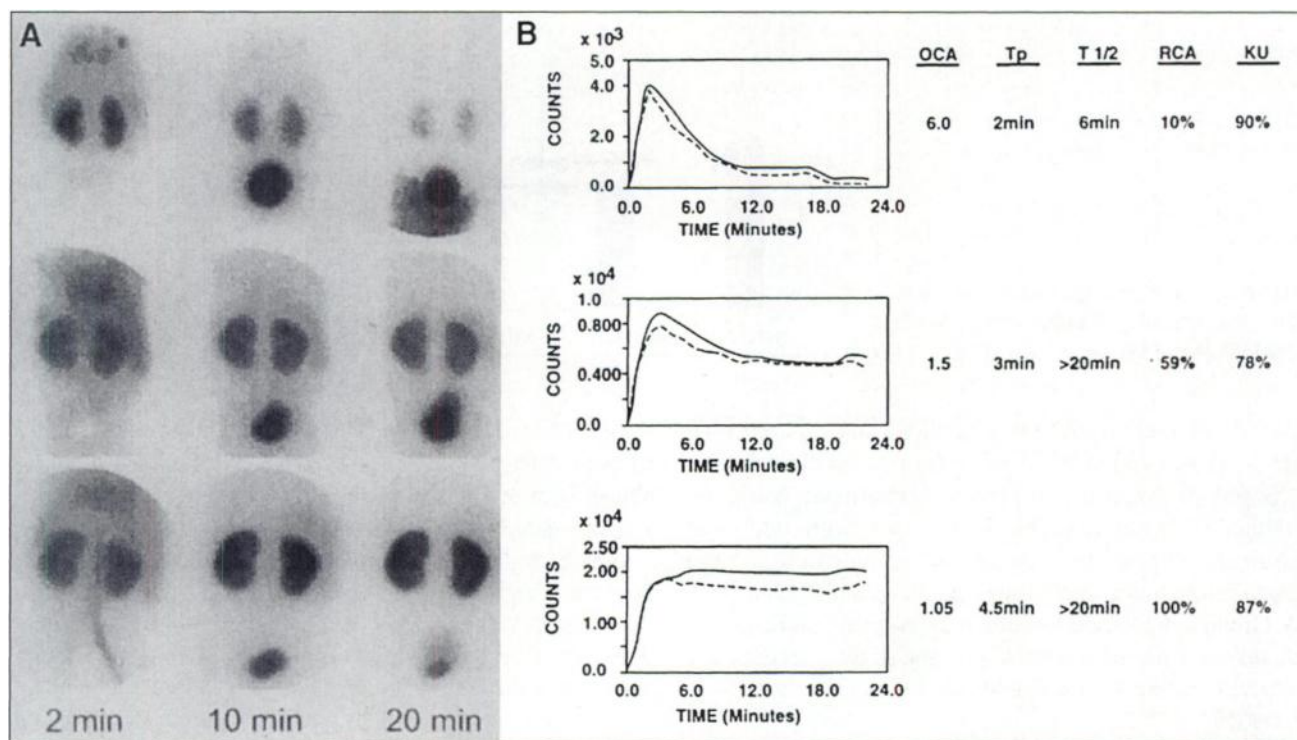
Of the 21 HIVN patients examined, 17 had undergone concurrent renal sonography, the results of which were reviewed and correlated with scintigraphy and renal function. The sonographic studies were interpreted as suggestive or not of HIVN on the basis of kidney size, echogenicity, corticomedullary differentiation, and pelvicalyceal thickening. The original interpretations by pediatric radiology specialists familiar with HIVN were used for this report. The sonograms were reviewed with knowledge of the patient's disease.

Statistical analysis was performed using the Student *t* test when comparing scintigraphic data between HIVN patients and control patients (Table 1). Scintigraphic data in the 3 groups of HIVN patients were compared with individual CrCl values using 1-way ANOVA (Table 2) and the Tukey post-test probability for multiple comparisons.  $P < 0.05$  was considered significant.

## RESULTS

Eighteen of the diuretic MAG3 studies and renograms of patients with HIVN looked different from the control studies by the consensus of the 2 reviewers (Figs. 1A and B). To the observer familiar with MAG3 pediatric studies, the kidneys in HIVN patients appeared larger than normal (in relation to the size of the body), the contrast of the kidney-to-background activity at 2 min was frequently reduced, and the parenchyma remained distinctly hyperactive at 20 min (Fig. 1A). The renograms of HIVN patients were flat, with delayed peaking and slowly decreasing activity; the tubular radiopharmaceutical was retained longer, to the extent that, at 20 min, cortical activity was much higher than on control renograms (Fig. 1B). The abnormality was bilateral, symmetric, and diffuse within the resolution limits of the method, involving the entire parenchyma of the kidneys without differentiation of cortex and medulla. Emptying of the drainage system after hydration and the use of diuretic was normal in all kidneys; the differential function (or split renal function) was within normal limits (45%–55%).

Objectively, all semiquantitative variables, as a group, studied in patients with HIVN were shown to be statistically different from control variables by the Student *t* test (Table 1; Fig. 2). The relative size of the kidneys of patients with HIVN was greater than that of control patients; the kidneys accumulated less MAG3 (lower KU), peaked later (higher Tp), and discharged the activity more slowly (higher T 1/2 and RCA). OCA was decreased, denoting both a decrease in



**FIGURE 1.** (A) Selected images of scintigraphic studies in control patients (top row) and in 2 patients with HIVN, moderate (middle row) and severe (bottom row). (B) Renograms and semiquantitative variables for same patients as in (A).

the uptake and a delay in the discharge of radioactivity. These values were abnormal in all but 2 of the HIVN cases and in 2 HIV patients without HIVN.

In 2 patients with HIVN, scintigraphy and sonography had normal findings. The patients were 2 and 5 y old. In 1 of them, the sole manifestation of nephropathy was proteinuria; in the other, nephropathy was manifested through renal tubular acidosis and proteinuria. Both had mild renal impairment shown by CrCl and abnormal results on follow-up MAG3 scintirenoigraphy, as described for the other

HIVN patients with increased proteinuria. On the other hand, in 2 HIV-positive patients without clinical or laboratory manifestations of renal disease including proteinuria and with normal sonographic findings, scintigraphy had abnormal findings, with the same pattern as in patients with HIVN. These patients manifested proteinuria later and, for this reason, were included in the study but considered as a separate subgroup (Table 1).

Semiquantitative variables on MAG3 scans in relation to the degree of renal impairment (by creatinine levels) are

**TABLE 1**  
Comparison of Semiquantitative Variables of Diuretic MAG3 Scintirenoigraphy Between HIV-Positive Children With and Without HIVN and Control Patients

Subjects	Kidney size*	Tp (min)	T 1/2 (min)	RCA† (% of peak)	OCA‡ (% of 20 min)	KU§ (60–120 s)
Patients with HIVN (n = 21)	63.5 ± 7.2 (50–81)	5.1 ± 3.5 (3–14)	12 ± 7.2 (6–20)	51.3 ± 27.9 (10–99)	2.6 ± 2 (0.65–3.65)	77.2 ± 12.9 (48–90)
Patients without HIVN (n = 2)	50, 67	3, 3	6, 6	12, 12	5.3, 6	52, 80
Control patients (n = 10)	50.4 ± 6.2 (22–60)	2.7 ± 0.6 (2–3.5)	4.4 ± 2.1 (7–9)	15.7 ± 3.4 (9–20)	4.5 ± 0.8 (3.3–6)	84.4 ± 1 (77–95)
P	0.00047	0.0022	0.00056	0.000032	0.00052	0.017

\*Ratio of combined width of kidneys/width of body.

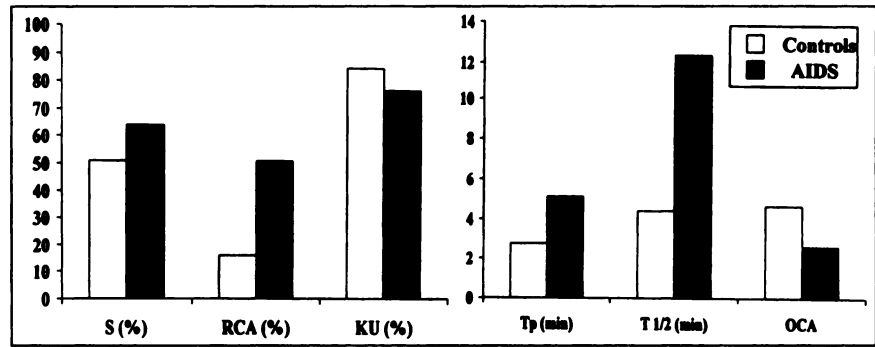
†Activity at 20 min × 100/peak time.

‡Activity at 2.5 min/20 min.

§Ratio of kidney activity to kidney + background activity at 60–120 s.

||Value between HIVN patients and control patients, using Student *t* test.

Values are mathematic mean ± SD, with range in parentheses; in patients without HIVN, individual values are indicated.



**FIGURE 2.** Semiquantitative variables in control patients and all patients with HIVN as 1 group. S = size.

shown in Table 2. By ANOVA, a significant difference (F score > 1) was found in all variables (except size) among the 3 groups by degree of renal impairment based on individual CrCl values (Table 2). Group 1, with mild renal impairment, differed from the other 2 groups in T 1/2 and RCA and from the severely impaired group 3 in Tp and OCA also. Group 2, with moderate renal impairment, and group 3, with severe renal impairment, did not show a statistically significant difference except in Tp, although a trend was present (Fig. 3).

Of the 17 sonographic studies performed at the time of scintigraphy in the HIVN patients, only 10 were reported to have abnormal results. Only patients with moderate to severe renal impairment had enlarged, echogenic kidneys with loss of corticomedullary differentiation. Sonographic findings did not correlate with MAG3 or with severity of renal impairment.

Of the 23 patients, 7 underwent follow-up scintigraphic

studies (4 had 2 and 3 had 3 studies). All follow-up studies showed deterioration in some of the semiquantitative variables (RCA or OCA). However, for the comparative analysis, only data from the first study were used.

Finally, MAG3 scintigraphic studies helped exclude other congenital or acquired diseases (obstructions, hypoplasia, multicystic kidney, focal parenchymal dysplasias, infections, or scars) (13,14). This ability was useful in the selection of the population for this analysis, because in many cases, sonography either was not performed or showed questionable findings in congenital disorders, such as fullness of pelvis or obstruction.

## DISCUSSION

Renal MAG3 studies in pediatric patients with HIVN revealed abnormal imaging characteristics and changes in semiquantitative scintigraphic variables indicating deterioration of renal function. Such variables in HIVN patients were

**TABLE 2**  
Comparison of Semiquantitative Scintigraphic Variables Among 3 Groups of Patients

Renal impairment	Kidney size*	Tp (min)	T 1/2 (min)	RCA† (% of peak)	OCA‡ (% of 20 min)	KU§ (60–120 s)
Group 1, mild (n = 10)	61.2 ± 6.6 (52–72)	3.5 ± 0.6 (3–5)	7.8 ± 4.2 (6–10)	31.5 ± 15.5 (10–43)	3.6 ± 2.12 (1.4–3.5)	80.8 ± 9.9 (74–90)
Group 2, moderate (n = 5)	66.2 ± 12 (52–74)	5.8 ± 3.6 (4–7)	16.6 ± 7.1 (12–20)	74.2 ± 15.8 (40–90)	1.5 ± 0.74 (1.2–2.1)	69.2 ± 17.6 (48–83)
Group 3, severe (n = 6)	64.5 ± 1.6 (50–81)	9.1 ± 4.7 (5–14)	9.6 ± 0.8 (8–20)	82.33 ± 14.67 (56–99)	0.98 ± 0.36 (0.65–2.5)	79.5 ± 12.94 (54–80)
ANOVA						
F score	0.77	6.402	6.526	25.10	6.34	1.45
P¶						
Gr 1/Gr 2	NS	NS	<0.01	<0.001	NS	NS
Gr 1/Gr 3	NS	<0.01	<0.005	<0.001	<0.05	NS
Gr 2/Gr 3	NS	<0.05	NS	NS	NS	NS

\*Ratio of combined width of kidneys/width of body.

†Activity at 20 min × 100/peak time.

‡Activity at 2.5 min/20 min.

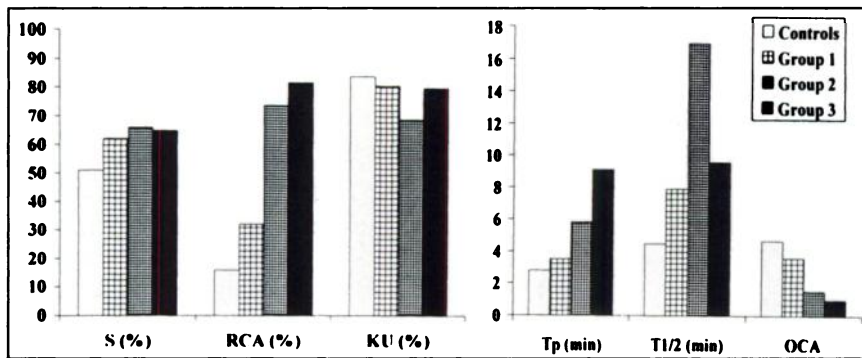
§Ratio of kidney activity to kidney + background activity at 60–120 s.

||F > 1 means that variable being tested is affected by CrCl.

¶P < 0.005 means significant difference exists between various subgroups in relation to individual CrCl.

NS = not significant.

Values are mathematic mean ± SD, with range in parentheses. Creatinine clearance: group 1, 50–100; group 2, 25–50; group 3, <25 mL/min/1.73 m<sup>2</sup>.



**FIGURE 3.** Semiquantitative variables in control patients and 3 groups of HIV patients on basis of severity of impairment of renal function (group 1, CrCl > 50; group 2, CrCl = 25–50; and group 3, CrCl < 25 mL/min/1.73 m<sup>2</sup>). S = size.

found to be statistically different from those in control patients. These findings, observed with a tubular scintigraphic agent, most probably reflected a diffuse parenchymal disorder with tubular involvement. The use of furosemide at the time of injection of the radiopharmaceutical guaranteed that the abnormally retained activity observed in the kidneys in HIVN patients was true parenchymal activity and not activity pooled in the calyces or the collecting tubules, a fact that was also seen on the images from 6 min to the end of the study (Fig. 1A). The control patients were representative of the HIV patients for age, and all had normal findings based on the literature and the experience in this laboratory (peak at 2–3 min, RCA < 20% except in neonates, in whom RCA was <50%).

The semiquantitative variables chosen for analysis provided objective information about abnormalities in the rate of accretion (accumulation) of the imaging agent by tubular cells (KU at 60–120 s); the speed of processing and rate of early secretion of the agent by the tubular cells (Tp and T 1/2); and the RCA, which reflected the rate of late secretion. OCA reflected both the rate of accretion and the rate of processing and discharge of the activity and was useful in stratifying patients with plateauing or rising renograms in which RCA was always 100%. All these values were found to be abnormal in HIVN patients, although accumulating and secretory functions, which agreed somewhat with one another, were not proportionately involved.

Decreased accumulation of activity may be a consequence of a decrease in renal blood flow or of tubular hypofunction or damage. On the other hand, the parenchymal retention found in HIVN appears not to be a simple kinetic phenomenon, caused by decreased early uptake and continuous supply of MAG3 by plasma, but rather an intrinsic dysfunction. The retention happens in other conditions (e.g., renovascular hypertension and renal vein thrombosis) and after decompression of obstruction unilaterally, with normal plasma clearance by the contralateral kidney. Whether parenchymal retention is an indirect consequence of a relatively more severe impairment of glomerular filtration rate than tubular function or is caused by derangement of tubular cell function (more severe impairment in the secretion than in the uptake of MAG3) remains to be determined. The tubules should be the site of parenchymal retention (the tubular cells or the lumen), because MAG3 is taken up

mainly from the peritubular interstitium (supplied by the second capillary network) and excreted by the tubular cells.

A deterioration of renoscintigraphic variables was also observed as CrCl decreased from greater than to less than 50 mL/min/1.73 m<sup>2</sup>. The absence of gradual (linear) deterioration in all scintirenographic variables with a decrease in CrCl below 50 mL/min/1.73 m<sup>2</sup> is probably multifactorial. Most important, stratification by CrCl does not necessarily reflect tubular function, which is mainly studied using MAG3. In addition, in more severe renal impairment, changes in the renograms are attributable to several causes, including decreased blood flow; continuous availability of MAG3 in the blood pool because of renal failure; decreased GFR, which alters the dynamics of kidney function and urine production; and impaired secretion by tubular cells. Renal function in HIVN patients may be overestimated by CrCl because of malnutrition or worsening renal function leading to tubular secretion of creatinine. Conversely, decreased effective renal blood flow and concomitant renal injury may lead to underestimation of glomerular function by MAG3.

Two patients had proteinuria (diagnosed as HIVN) and normal MAG3 findings, and 2 HIV patients had abnormal MAG3 findings and no HIVN. We could not firmly characterize these patients, because renal biopsies were not obtained for all the patients. The data do not make clear whether proteinuria precedes the abnormal scintigraphic findings or follows them. A prospective study is needed to evaluate how frequently MAG3 scintirenographic results are abnormal in the general HIV-positive and AIDS populations, before the development of clinical manifestations of nephropathy (such as persistent proteinuria) and, conversely, how frequently HIVN proteinuria is present without abnormal MAG3 findings.

The experience at our center and other centers (15) is that similar scintigraphic abnormalities are present in other types of parenchymal disorders that are manifested with either a diffuse homogeneous or a multifocal pattern. Examples are congenital dysplasia, acute or chronic diffuse parenchymal diseases in the native kidneys, and renal transplants (including acute tubular necrosis, drug toxicity, glomerulopathy, systemic lupus, allograft rejection, and some infections) (13,14). Similar to retained <sup>67</sup>Ga renal cortical activity in HIVN (16,17), the diffuse parenchymal dysfunction on

MAG3 diuretic scintirenograms appears to be a nonspecific consequence of a diffuse parenchymal disease.

Seventeen patients in this study underwent concurrent renal sonography, 10 with abnormal results and 7 with normal results. This finding seems to indicate greater sensitivity for scintirenoigraphy than for sonography. However, because of the selection of the population and the randomness with which sonography was performed, one may not conclude that MAG3 scintirenoigraphy is more sensitive than sonography in indicating diffuse parenchymal disease in general and in HIVN specifically. Renal deterioration was shown by the variables studied in follow-up scintigraphy, whereas follow-up sonography may not easily show objective signs of deterioration. However, the number of studies is limited and no final conclusions can be drawn.

Because HIVN is, at present, diagnosed through laboratory tests, the need for imaging is marginal. Sonography is quick and noninvasive and may exclude most congenital anatomic disorders. Scintigraphy corroborates evidence of HIVN and helps in the further examination of patients for congenital disorders found or suggested by sonography, in the confirmation and quantification of obstruction, and in the diagnosis of acute pyelonephritis and other acquired diseases (13,14,18). The evaluator has to know the MAG3 findings for HIVN to attribute them correctly to that disease and not to other diseases. However, should specific treatment for HIVN become available, MAG3 diuretic scintigraphy, after further prospective confirmation, may provide a sensitive way to accurately evaluate the progression of disease and the effectiveness of therapy.

Administering a diuretic with MAG3 produces accurate cortical data by emptying the drainage system and substantially reduces radiation exposure to the critical organ, the bladder (18). In addition, if this test is to be administered for diagnosis and follow-up of HIVN exclusively, the dose of MAG3 may be reduced substantially, to as low as one tenth of the usual dose (19). Finally, we have observed, in adult HIV-infected patients, findings similar to those for MAG3 scintigraphy in children with HIVN.

## CONCLUSION

Diuretic MAG3 scintigraphy showed characteristic, although not entirely specific, abnormalities in patients with the clinical syndrome of HIVN, even in certain patients with normal sonographic findings. The abnormalities reflected a diffuse parenchymal dysfunction. Semiquantification of the data indicated a correlation between the severity of HIVN and the intensity of the scintigraphic findings. Knowledge of these findings is useful when performing scintigraphy for its standard indications. Scintigraphy can provide corroborative evidence of HIVN and appears to have potential for following the progression of disease and the effect of

treatment. Further study is needed of the specificity of the test in HIV patients without HIVN and the sensitivity of the test in HIVN patients.

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