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Renal Anomalies in Patients with Turner Syndrome: Is Scintigraphy Superior to Ultrasound?

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Renal anomalies are present in up to 30% of patients with Turner syndrome (TS). Renal ultrasound (U/S) detects anatomical renal anomalies only while renal scintigraphy detects anomalies, detects early renal malfunction, and estimates glomerular filtration rate (GFR). Thus, we aimed to assess frequency of renal abnormalities detected by scintigraphy in comparison to renal U/S in TS patients. Ninety TS patients were subjected to auxological assessment, measurement of serum creatinine; and renal U/S and scintigraphy. Renal U/S detected renal anomalies in 22.22% of patients versus 17.78 % detected by scintigraphy ($P = 0.035$). Scintigraphy detected renal functional abnormalities in 44.44% of patients in the form of subnormal total GFR, abnormal renogram curve pattern, improper tracer handling and perfusion; and difference in split renal function >10% between both kidneys. Patients with a 45,X karyotype had more renal functional abnormalities (56%) than those with mosaic karyotype (33.33%), $P = 0.04$. In conclusion, renal scintigraphy is not superior to U/S in detection of renal anomalies but is a reliable method for early detection of renal malfunction in TS patients especially those with 45,X to ensure early management to offer a better quality of life. © 2015 Wiley Periodicals, Inc.

Key words: anomalies; renal; scintigraphy; turner syndrome; ultrasound

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INTRODUCTION

Turner syndrome (TS) is a relatively common disorder, affecting ~1/2,500 female births. It is defined as deficiency of all or part of the second sex chromosome in phenotypic females resulting in some characteristic physical abnormalities including reduced final height, cardiovascular malformations, and premature ovarian failure [Jones et al., 2013].

Congenital malformations of the urinary system occur in up to 30% of patients with TS among which rotational abnormalities and double collecting systems are most frequent. Prior to 1980, intravenous pyelography (IVP) was the radiologic method used for initial screening, and subsequently, U/S has been used as the initial imaging technique. Therefore, all individuals with TS should have a renal U/S study performed at the time of initial diagnosis. If abnormalities are detected, further evaluation should be performed, and the appropriate therapy instituted [Lippe, 2009]. Most of renal anomalies detected previously by U/S and IVP were structural and anatomical, while functional anomalies, which indicate early nephropathy or nephrouropathy could not be detected reliably or quantified by such modalities [Boubaker et al., 2006; Lippe, 2009].

Renal scintigraphy refers to serial imaging after intravenous administration of technetium-99 m DTPA or technetium-99 m MAG3. It is not as operator dependent and subjective as U/S, it is also relatively inexpensive and non invasive technique with minimal radiation dose and provides an accurate estimation of GFR. It is used for qualitative and quantitative evaluation of differential renal function. It is considered a very sensitive method for early functional changes indicating early nephropathy [Boubaker et al., 2006].

Thus, the current study aimed to assess the frequency of renal abnormalities detected by scintigraphy in comparison to those detected by renal U/S in TS patients. Moreover, this study

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highlights the role of scintigraphy in early detection of renal malfunction in TS patients as well as calculation of split kidney function.

MATERIALS AND METHODS

Study Population

This cross sectional study was conducted on 90 TS patients with a mean age of 12.86 ± 4.54 years (2–28 years). All patients had a clinically female phenotype and their karyotype was consistent with TS. They were recruited from Nile Hospital, Egyptian Health Insurance during September 2013–May 2014.

An informed written consent was signed by the parents or legal guardians of the subjects or by the subject herself. This study was approved by the Ethics Committee, Faculty of Medicine, Ain Shams University, Cairo, Egypt, which complies with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

Methods

All patients were subjected to the following:

(1) Clinical assessment: With special emphasis on history of drug intake and family history of renal anomalies or diseases.
(2) Auxological assessment: Height and weight were measured; height for age Standard Deviation Score (SDS) was calculated according to the norms of Tanner et al. [1966]; and Ranke et al. [1983] reference values for TS. Weight for height SDS was calculated according to the norms of Tanner et al. [1966].
(3) Tanner pubertal staging: The breast stage was determined according to the standards of Tanner and Whitehouse [1976].
(4) Laboratory assessment:
- Karyotype was Obtained From Patients Records.
- Serum creatinine.

(5) Radiological assessment:
- Renal and pelvic ultrasonography was performed with the Esaote My lab twice machine using the abdominal low frequency (2.5–5MHz) transducer. The patient should be well hydrated, and is asked to drink adequate amount of clear fluids before the procedure. The patient should lie in a supine position exposing the abdomen. Both kidneys are scanned anterolaterally. Both anteroposterior and transverse dimensions are measured for each kidney as well as the parenchymal thickness. Kidney length should be within 2 cm of each other. A difference greater than 2 cm suggests that either one kidney is too small or too large. The cortical echogenicity is normally equal or somewhat less than that of the liver and less echogenic than the spleen. The pyramids are hypoechoic structures being less echogenic than the cortex. A note was made of parenchymal echogenicity or hydronephrosis or anatomic renal anomalies including ectopic, horseshoe kidney, double collecting system, a non visualized kidney, and a small kidney with decreased corticomedullary differentiation [Lee, 2004].
- Renal scintigraphy:

I. Patient preparation:
  - No special preparation was needed apart from intravenous fluids intake 30–60 min before injection (10–15 ml/kg over 30 min).
  - Voiding before injection.
  - Voiding after end of study.
  - The patient was advised to keep a distance of 2–3 m from other family members for 24 hr.

II. Procedure:
  - Patient is kept in supine position.
  - 0.1–0.2 mCi/Kg of TC 99 m DTPA (minimum 1 mCi, Maximum 5 m ci) are injected intravenously.
  - Phillips Gamma Camera with low energy all—purpose (LEAP) collimator is used.
  - Technique includes dynamic acquisition of 1–2 sec images for 1 min (vascular phase), followed by administration of furosemide 0.5 mg/kg (1 mg/kg for children) with a maximum dose of 40 mgs, then 15–60 sec images for 20–30 min (functional uptake, cortical transit, and excretion phases) are taken.
  - The regions of interest are typically drawn around the whole kidneys, but occasionally are limited to the renal cortex if considerable amount of collecting system activity is present.
  - A background region of interest is placed adjacent to each kidney depending on regions of interest drawn, the time activity curve will reflect the functional clearance of whole kidney, renal cortex, or collecting system.
  - The differential renal function is calculated based on the relative counts accumulated in each kidney during the second minute after injection of furosemide.

Abnormal renal findings by scintigraphy were described in the form of:
  - Delayed or poor tracer handling of one or both kidneys.
  - Abnormal renogram (curve pattern, amplitude, and time sequences).
  - Total GFR < the normal value for given age and sex according to NKF-KDOQI clinical practice guidelines for chronic kidney disease [2002]. GFR was calculated using the following equation: GFR (ml/min/1.73 m2) = (0.41 × Height in cm)/Creatinine in mg/dl.
  - Increased extra renal background activity.
  - Difference in split renal function >10% between both kidneys.
  - Anatomic renal anomalies including ectopic kidney, horseshoe kidney, double collecting system, a non visualized kidney, and a small kidney with decreased corticomedullary differentiation.

Statistical Analysis

The results were analyzed using the Statistical Package for the Social Science (SPSS) version number 10, Echosoft corp; 2005. Description of quantitative variables was in the form of mean ± standard deviation and range while that of qualitative variables was in the form of frequency and percentage. Spearman correlation coefficient test (r-test) was used to rank different variables against each other either directly or indirectly. A *P*-value of <0.05 was considered significant.

RESULTS

Descriptive Data of TS Patients

Descriptive data of TS patients and the frequency of various karyotypes are shown in Tables I and II. Regarding Tanner breast staging, of the 90 studied cases, 32 (35.56%) were in Tanner stage 1, 22 (24.44) were in Tanner stage 2, 16 (17.78%) were in Tanner stage 3, 12 (13.33%) were in Tanner stage 4, and 8 (8.89%) were in Tanner stage 5. Serum creatinine of all patients was within the normal reference range for age (<1.2) mg/dl.

Radiographic Findings of TS Patients

Renal anomalies were detected by U/S in 20/90 patients (22.22%) and by renal scintigraphy in 13 patients [17.78%, $P=0.035$]. Frequency of renal anomalies detected by U/S compared to scintigraphy is shown in Table III. Renal functional abnormalities by renal scintigraphy (in the form of subnormal total GFR, abnormal renogram curve pattern, improper tracer handling, and perfusion as well as difference in split renal function >10% between both kidneys) were detected in 40 cases (44.44%). Moreover, the frequency of subnormal GFR was more among TS patients with renal anomalies detected by U/S than those with normal ultrasound (U/S). Relation between ultrasonographc findings and GFR among TS patients is presented in Table IV.

Relation Between Karyotype and Characteristics of TS Patients

On comparing 45,X (n = 50) to mosaic group (n = 24), all auxological parameters and Tanner stages did not differ between groups ($P>0.05$). In spite of the fact that the frequency of renal anomalies by U/S was more frequent among 45,X than in the mosaic group 14/50 (28%) versus 4/24 (16.67%), respectively, it did not reach a statistically significant level ($P=0.06$). Among the fourteen 45,X patients with renal anomalies, 4 (28.58%) had horseshoe kidney, 4 (28.58%) had pelvic kidney, 2 (14.28%) had double collecting system, and 2 (14.28%) had non visualized left kidney, and 2 (14.28%) had small left kidney with decreased corticomedullary differentiation (Figs. 1 and 2). Among the four mosaic cases found to have renal anomalies by U/S, two had horseshoe kidney (50%), while double collecting system was found in the other 2 (50%). Moreover, two patients with 46,X,iX(q) karyotype had double collecting system by U/S. Subnormal GFR and renal functional abnormalities by scintigraphy were more frequent in 45,X than in the mosaic group 28/50 (56%) versus 8/24 (33.33%), $P=0.04$ (Fig. 3). Four patients with 46,X,iX(q)and 45,X/46X,+r(X) karyotype had subnormal GFR.

TABLE I. Descriptive Data of Studied Patients (n = 90)

	Mean ± SD	Range
Age (years)	12.86 ± 4.54	2–28
Height for age SDS [Tanner[a]]	−3.99 ± 0.84	113.5–150.1
Height for age SDS [Ranke[b]]	−0.95 ± 0.74	−2.08 to +1.35
Weight for height SDS [Tanner[a]]	+2.64 ± 1.36	−0.15 to +5.56
Total GFR (mL/min)	105.82 ± 24.03	62.9–168

SDS, standard deviation score; GFR, glomerular filtration rate; TS, turner syndrome.
[a]Tanner et al. [1966].
[b]Ranke et al. [1983].

TABLE II. Karyotype Distribution Among TS Patients (n = 90)

Karyotype	N	%
45,X	50	55.56
45,X/46,XX	24	26.67
46,X,iX(q)	6	6.67
46,X,del(Xp)	3	3.33
45,X/46,X,+r(X)	2	2.22
45,X/46,X,+mar	2	2.22
45,X/46,X,i(Xq)/47,XX,i(Xq)	2	2.22
46,XX/46,X,i(Xq)	1	1.11

TS, turner syndrome.
Results are expressed as frequency and percentage.

Relation Between Age and Renal Function in TS Patients

Ultrasound (U/S) findings were not affected by age among TS Patients ($P=0.11$). On the other hand, there was a significant negative correlation between age and GFR ($r=0.92$, $P=0.01$). The mean age of studied subjects with subnormal GFR (n = 40, 13.4 ± 2.3 years) was significantly higher than that with normal GFR (n = 50, 6.80 ± 1.70, $P<0.01$). In spite of the presence of normal GFR in 50 patients, 20 patients (40%) showed a difference between the renal contribution percentage of >10%.

DISCUSSION

Turner syndrome affects about 1:2,500 female newborns due to partial or total loss of second sex chromosome [Jones et al., 2013]. It is characterized by an increase in the frequency of congenital anomalies, mainly cardiovascular and renal, contributing to morbidity and mortality of these patients [Lippe, 2009].

In this study, our concern was early detection of an effect on renal function among our TS patients by renal scintigraphy since

TABLE III. Frequency of Renal Anomalies Among TS Patients (n = 90) Detected by U/S Compared to Scintigraphy

	Ultrasound	Scintigraphy		
Renal anomalies	**N (%)**	**N (%)**	**X2**	***P***
Total	20 (22.22)	16 (17.78)	8.66	0.035*
Horseshoe kidney	6 (6.67)	5 (5.56)	2.55	0.09
Pelvic kidney	4 (4.44)	4 (4.44)	1.01	0.21
Double collecting system	6 (6.67)	5 (5.56)	3.10	0.08
A non visualized kidney	2 (2.22)	1 (1.11)	3.71	0.10
A small kidney with decreased corticomedullary differentiation	2 (2.22)	1 (1.11)	3.71	0.1

U/S, ultrasound.
Results are expressed as frequency and percentage.
*$P < 0.05$.

renal U/S detects only morphological and structural anomalies but is insensitive in detection of functional anomalies [Boubaker et al., 2006; Lippe, 2009].

Caravalho et al. [2010] found that 29.3% of TS patients had renal anomalies after being evaluated by U/S and intravenous urography which is slightly higher than our results. Most congenital anomalies detected were structural or anatomical [Caravalho et al., 2010]. They stated that structural renal anomalies were not associated or related to the karyotype which was confirmed in the current study. Bilge et al. [2000] stated that about 30–40% of their TS patients had renal problems. They were investigated by many modalities.

In our study, all 90 TS patients were asymptomatic with normal serum creatinine. When performing renal U/S, 20 patients (22.22%) had renal malformations in the form of horseshoe kidney in 6 (30%), pelvic kidney in 4 (20%), double collecting system in 6 (30%), non visualized left kidney in 2 (10%), and small left kidney with decreased corticomedullary differentiation in 2 (10%). In addition, our study highlighted the fact that scintigraphy was not superior to U/S in detection of renal anomalies in TS patients.

On the other hand, when renal scintigraphy was performed, 40 patients (44.44%) had renal dysfunction, twice that of anatomic anomalies detected by renal U/S. The abnormal renal findings by scintigraphy included delayed or poor tracer handling of one or both kidneys, abnormal renogram (curve pattern, amplitude, and time sequences), a total GFR < the normal value for given age and sex according to NKF-KDOQI guidelines [2002], increased extra renal background activity, a difference in split renal function >10% between both kidneys, and ectopic malfunctioning kidney. Decrease in the total GFR or abnormal differential renal function denotes underlying renal pathology. Many studies confirm the accuracy of measurement of GFR and split kidney function using renal scintigraphy [Gates, 1983]. In spite of 50 patients having a normal GFR, 20 (40%) had a renal contribution difference of more than 10% making asymmetric renal function one of the earliest indicators of future renal dysfunction. The frequency of subnormal GFR was higher among TS patients with renal anomalies detected by U/S than those with normal U/S.

Frequency of renal anomalies by U/S was not affected by age while age correlated negatively with GFR meaning that total GFR decreased with increasing age.

A study conducted by Gates [1983], revealed that renal scintigraphy GFR correlates extremely well with 24 hr creatinine clearance and is highly reproducible. Their study was conducted on 500 patients and provided valuable accurate information. Shore et al. [1984] performed a study on 50 children using Tc-99 m-DTPA renograms and GFR measured simultaneously by plasma disappearance. This method can accurately estimate GFR from the renogram in children. In a study conducted by Itoh [2003] on 133 patients, Gates' method and predicted creatinine clearance were compared with plasma clearance for the measurement of GFR. He stated that the Gates method correlates well with the Plasma sample clearance (PSC) method [Itoh, 2003].

TABLE IV. Relation Between Ultrasonographc Findings and GFR Among TS Patients (n = 90)

	Normal GFR	Subnormal GFR		
	(N = 50)	**(N = 40)**	**X2**	***P***
Normal U/S (n = 70)	44 (62.86)	25 (37.14)	14.66	0.0001[a]
Renal anomalies by U/S (n = 20)	6 (30)	14 (70)		

U/S, ultrasound.
Results are expressed as frequency and percentage.
[a]$P < 0.001$.

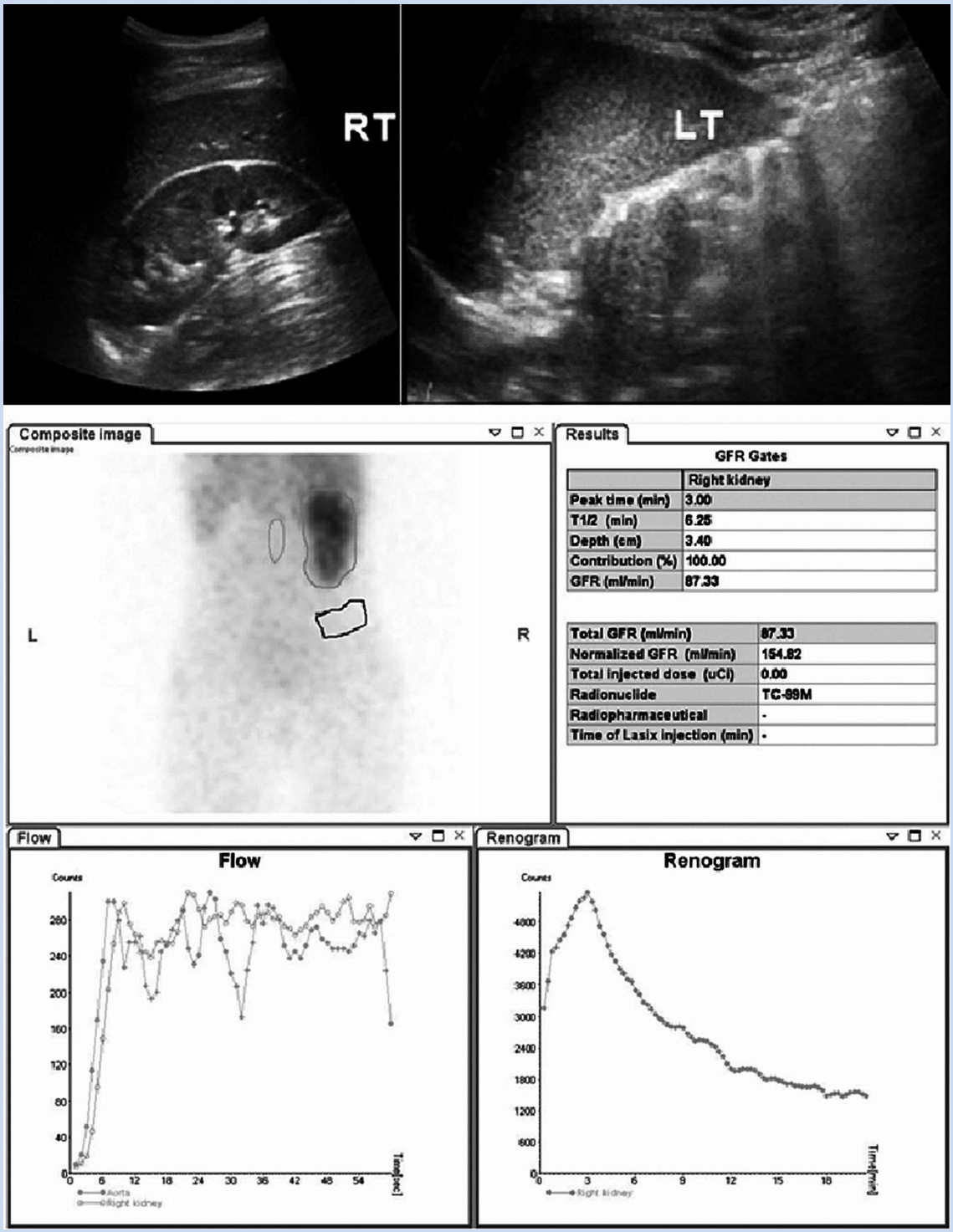

FIG. 1. Renal ultrasound and scintigraphy of an 11 years old TS patient with 45,X karyotype and normal serum creatinine. Renal ultrasound revealed normal right kidney and non visualized left kidney. Renal scintigraphy confirmed the absence of the left kidney and provided additional information about the remaining single kidney. It revealed decompensated overall renal function as well as decreased amplitude of the right renogram, which necessitates regular follow up for this patient.

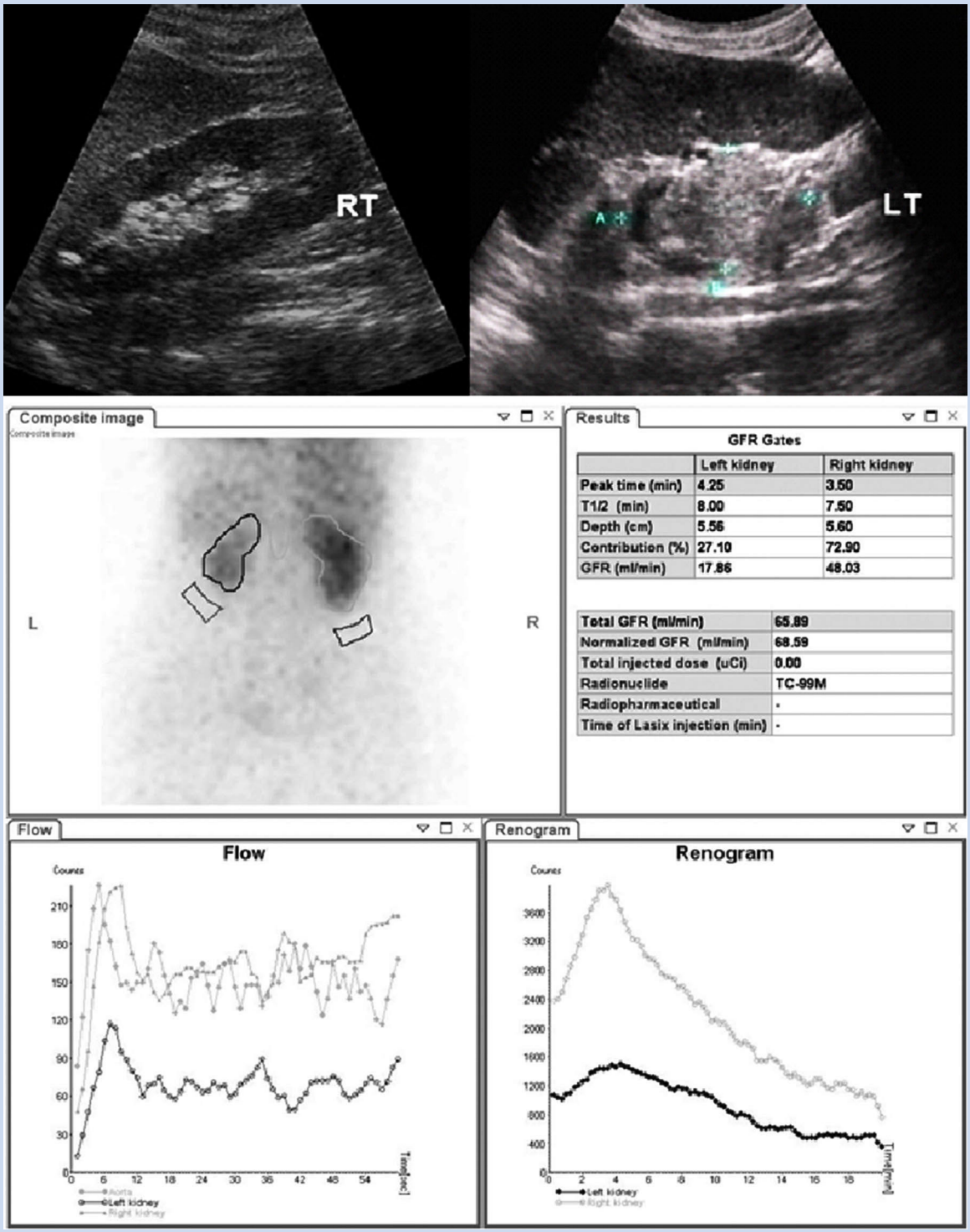

FIG. 2. Renal ultrasound and scintigraphy of a 20-year-old TS patient, 45,X karyotype, with normal serum creatinine. Renal ultrasound revealed normal right kidney and small left kidney with decreased corticomedullary differentiation. Renal scintigraphy confirmed the ultrasound findings and added extra information about the overall renal function. The left kidney was poorly perfused and improperly handling the tracer with plateau left renogram. Overall renal function was deteriorated (total GFR = 65.89 ml/min) and difference between split kidney function was >10% (73–27 = 46%). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga]

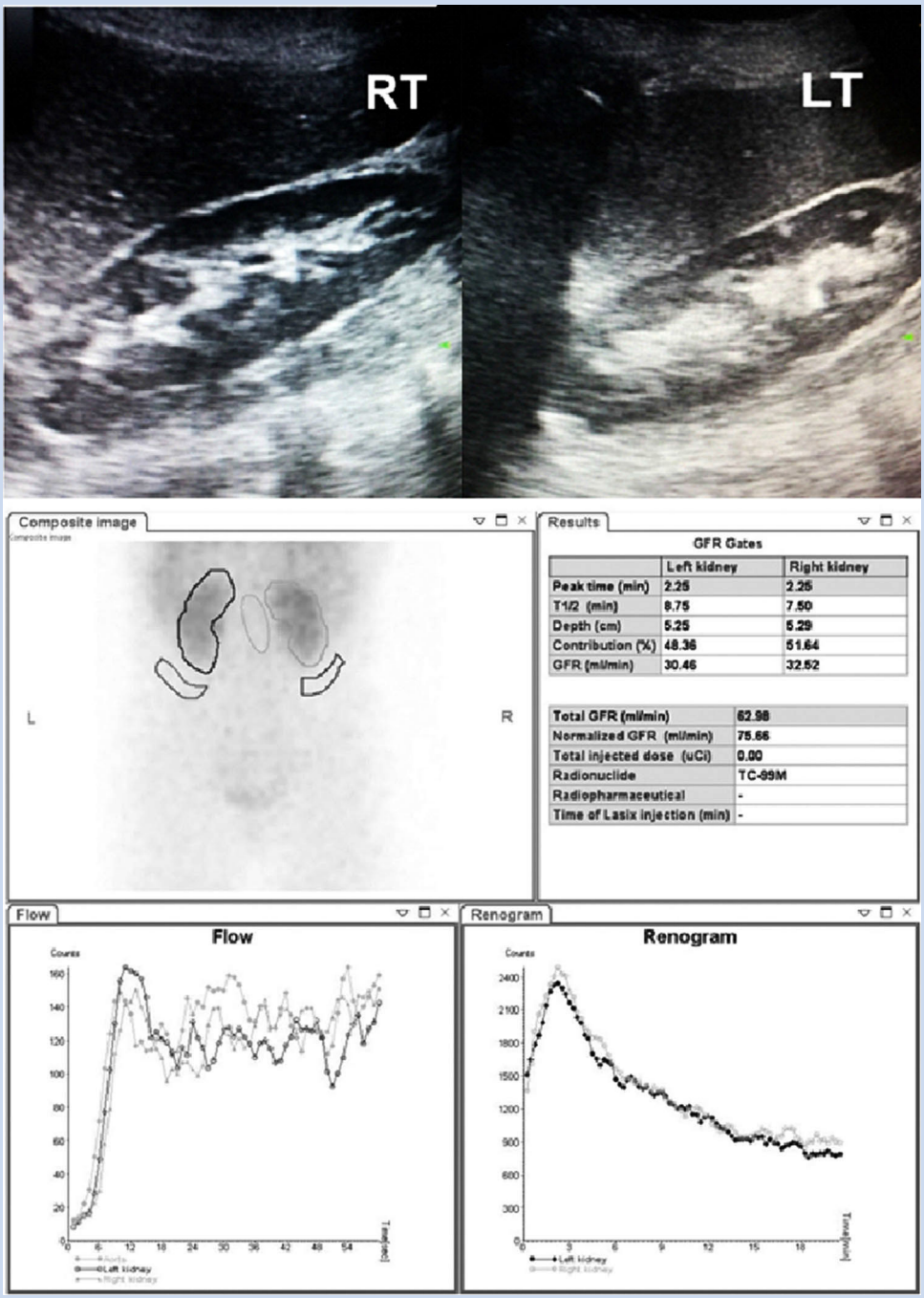

FIG. 3. Renal ultrasound and scintigraphy of an 18-year-old TS patient with 45,X karyotype. Serum creatinine and renal ultrasound were normal. Renal scintigraphy revealed subnormal total GFR values as well as low amplitude in both renograms, findings consistent with nephropathy. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga]

However, in a study conducted by Assadi et al. [2008], Tc-99 m DTPA renography was performed in 36 patients aged 18–72 years with a wide range of renal function (serum creatinine 1.37 ± 0.49 mg/dl). GFR was determined by four methods: the gamma camera uptake with low-dose Tc-99 m DTPA (Gates, LD); the gamma camera uptake with high-dose Tc-99 m DTPA (HD); the predicted creatinine clearance (Cockcroft–Gualt, CG); and the plasma sample clearance (PSC) method using a mono-exponential curve [Assadi et al., [2008]. The three methods were in agreement with the PSC, but the high-dose GFR method resulted in less error in estimation of GFR. Furthermore, GFR measurement and diuretic renography could be performed at the same time when the

high-dose method was used. Because of the low cost and negligible radiation burden, this method might be preferred for routine practice in nuclear medicine [Assadi et al., 2008].

From the above studies, we decided to depend on Tc-99 m-DTPA for measurement of GFR in our patients. Our study revealed that abnormal GFR values were consistent with other abnormal findings in renal scintigraphy.

Moreover, our study highlighted that abnormal renal scintigraphy was more frequent in TS patients with 45, X karyotype than those with mosaic karyotype. Our results were in agreement with a study by Flynn et al. [1996] who stated that TS patient with 45,X karyotype are at a higher risk in developing renal anomalies.

It is worth mentioning that normalized GFR was one limitation in our study as it wasn't consistent with other findings such as kidney split function, renograms, and total GFR. In most cases, the normalized GFR value was higher than the normal GFR range for the patient's age, although these patients had abnormal total GFR, renogram, and abnormal diferential renal split function. We didn't use on the normalized GFR, but depended on the Total GFR and other abnormal findings which were consistent with each other.

CONCLUSIONS

Renal scintigraphy is not superior to U/S in detecting renal anomalies, but it is a crucial imaging modality for TS patients, as it is an objective method providing additional data on the entire renal function. It detects hidden renal pathology early that may be missed on renal U/S. Moreover, even if GFR is within normal range, asymmetric renal function of more than 10% is a sensitive method for detecting future renal dysfunction, and necessitates regular follow up. The radiation dose is still a small one (0.1–0.2 mCi/kg) in comparison to other scintigraphic procedures like bone scintigraphy.

We recommend that TS patients (especially those with 45,X karyotype) should have a baseline scintigram after serum creatinine and renal ultrasound. If the scintigram is negative for any renal abnormality then no further investigation is necessary. But if the scintigram is positive for a renal abnormality, a regular follow up will be required. Early detection of renal abnormalities by scintigraphy will allow early intervention.

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