Potential diagnostic role of renal scintigraphy in the management of patients with high anorectal malformation

Chidambaram Natrajan Balasubramanian Harisankar[1] MBBS,
Bhagwant Rai Mittal[1] MD; DNB
Anish Bhattacharya[1] DNB;DRM
Hejjaji Venkataramarao Sunil[1] MD
Baljinder Singh[1] MSc; PhD
Katragadda Lakshmi Narasimha Rao[2] MS, MCh

1. Department of Nuclear Medicine
2. *Department of Pediatric Surgery Postgraduate Institute of Medical Education and Research, Chandigarh, 160 012, India*

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Correspondence address:
Dr. B.R. Mittal, Prof. and Head, Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, 160 012, India
Tel.: +91 172 275 6722
Fax: +91 172 2744401
E-mail: brmittal@yahoo.com

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Abstract

Urological problems are the leading associated anomalies in patients with anorectal malformation (ARM). In this study, we evaluated the role of scintigraphy in managing patients with high ARM. The records of infants with urologic anomalies on abdominal ultrasound and referred for scintigraphic evaluation were retrospectively analyzed. Diuretic renography in these patients was performed using ^{99m}Tc-diethyl triamine penta-acetic acid (^{99m}Tc-DTPA) or ^{99m}Tc-ethylene cysteine (^{99m}Tc-EC) while cortical scintigraphy was performed with ^{99m}Tc-dimercaptosuccinate (DMSA). Whenever available, EC was preferred in children of age less than 1 year. Forty patients (38 males, 2 females) were analyzed. The mean age of the population was 25 months (range 15 days-21 years). Eighteen of the forty patients were less than 3 months of age. Twenty seven of the patients were less than one year of age. The most common renal anomaly was unilaterally non-visualized kidney affecting 15 out of the 40 patients. The visualised kidney was abnormal in 8/15 patients. Hydronephrotic changes were noticed in 12 of 40 patients of whom 2 had pelvi ureteric junction obstruction that was confirmed and treated surgically. Horse shoe kidney was present in 1 patient while 2 had an ectopic kidney. Scarring/pyelonephritic changes were found in 7/40 patients. Five patients had already progressed to chronic renal failure at the time of scintigraphy. Only 8 patients of the 40 had bilaterally normal kidneys. *In conclusion,* this study suggests that urologic abnormalities often found in infants with high ARM may remain clinically silent and eventually lead to chronic renal failure. Proper evaluation by diuretic renography and cortical scintigraphy can lead to early identification of potentially treatable conditions hence reducing the likelihood of developing severe renal damage.

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Introduction

Anorectal malformation (ARM) is a developmental anomaly characterized by an absent or ectopic anus. It comprises a wide spectrum of disorders and involves the distal anus and rectum as well as the urinary and genital tracts. It affects children of both sexes and occurs in approximately 1 in 1500 to 5000 live births [1, 2]. Defects range from the very minor and easily treated with an excellent functional prognosis, to those that are complex, difficult to manage, often associated with other anomalies, and having a poor functional prognosis.

Malformations of other organ systems have been reported with an incidence varying from 30% to 70% with some being life threatening [3-8]. Though various organ systems can be affected, the genitourinary, cardiovascular, gastrointestinal and vertebral systems are the four most commonly involved in this group of patients. Urological anomalies are the leading abnormalities associated with ARM [8]. Urinary anomalies are observed up to 50%-60% of patients with high or intermediate forms and 15%-20% of low ARM [9]. Unlike genital anomalies, urologic anomalies are difficult to identify on clinical examination and form the primary cause of morbidity and mortality [10].

An abdominal ultrasound (USG) is a relatively cheap and first line investigation for identification of urological anomalies. However, it is a relatively non-specific investigation. Renal scintigraphy is a highly sensitive investigation for the evaluation of renal function. However, role of scintigraphy in patients with ARMs is not clearly defined in the literature. In a recent study, urologic anomalies were identified in about 11% of the patients who underwent scintigraphic evaluation [11]. This study was undertaken to evaluate the role of scintigraphy in managing patients with high ARM.

Subjects and methods

This study included a retrospective analysis of records of all the patients with high ARM referred to our department from the period of January 2005 to November 2008. The records of 40 patients were analyzed. Their mean age was 25 months (range 15 days to 250 months). Eighteen of the patients were less than 3 months old, while 27/40 patients were less than 1 year old. All patients included had already undergone corrective surgery for anorectal malformation. Patients with renal abnormalities on USG were referred to our nuclear medicine department for scintigraphic evaluation. A specific investigation like micturating cystourethrography (MCUG) was performed on patients with hydroureteronephrosis on abdominal USG or with evidence of repeated urinary tract infection (UTI). Patients who developed UTI were also referred for renal scintigraphy.

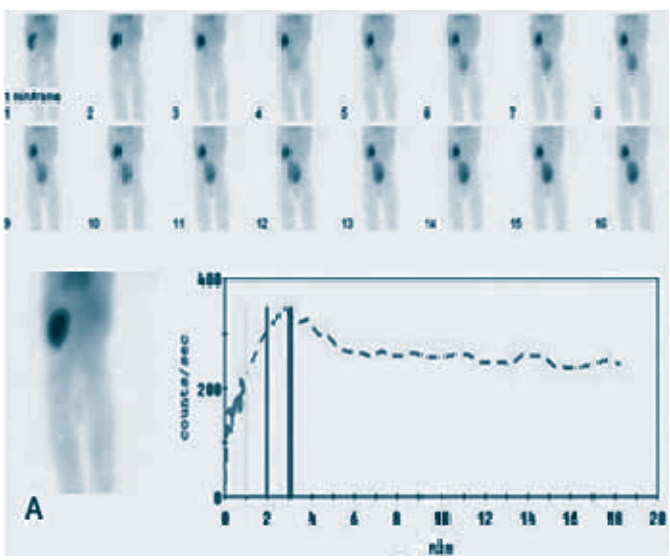
Scintigraphic evaluation of all 40 patients included both dynamic renography and cortical scintigraphy (24 of 40 patients). A total of 57 scans were performed in these 40 patients. These scans included technetium-99m diethyl triamine penta-acetic acid (^{99m}Tc-DTPA), ^{99m}Tc-ethylene cysteine (^{99m}Tc-EC) and ^{99m}Tc-DMSA cortical scintigraphy as indicated in Table 1. Whenever available, dynamic study using ^{99m}Tc-EC was preferred in children less than one year of age. Renal cortical scintigraphy was performed using ^{99m}Tc-DMSA. Follow-up renal scans were also performed in patients with pyelonephritic changes and in those with equivocal drainage. Seven patients with pyelonephritic changes/ cortical scars in either of the kidneys had repeat ^{99m}Tc-DMSA study. Ten patients had repeat dynamic renography. Of these patients, 2 had surgically proven pelvic-ureteric junction obstruction and repeat imaging was used to confirm the improvement in renal drainage. In the other 8 patients, repeated imaging was used for follow up of hydronephrotic change in either kidney. The patients were adequately hydrated by breast feeding and/or oral fluids as appropriate for their age. No intravenous rehydration was given. Babies younger than 5 months were not given any sedatives. Patients of age 5 months to 5 years were sedated orally with syrup triclofos in a dose of 75-100mg/kg body weight. Diuretic was administered along with the radiotracer in all patients above 3 months of age in a dose of 1mg/kg. Perfusion images were obtained at 2sec/frame for the initial 1min and parenchymal images were acquired at 1min/frame for the next 24min. Post void images and delayed images up to 3h were acquired after keeping the baby upright for at least 3min to assist gravity dependent drainage in this age group. Persistent retention of tracer in the renal pelvis till 3h was labeled as indication of an obstructed urinary system.

Cortical scintigraphy with ^{99m}Tc-DMSA included planar and pinhole images acquired 3h after tracer injection. Reduced tracer uptake without a break in cortical outline in patients with clinical evidence of UTI was considered indicative of a pyelonephritic change. A break in the cortical outline, especially when persistent on the follow-up scan, was labeled as scarring. Increased background tracer activity with poor cortical uptake was considered as compromised function. Unilateral relative renal function of less than 30% as compared to the other kidney was considered as impaired function.

Results

Data analysis of the 40 patients (80 renal units or locations) showed 31 renal units (38.75%) to be structurally and functionally normal. This included 16 units in 8 patients and 15 units in 15 other patients (1 kidney in each patient). The other kidney was either non-visualized or had some functional abnormality in these 15 patients. Figure 1 shows renal function evaluated with ^{99m}Tc-DTPA and ^{99m}Tc-DMSA in one of our patients (Table 1).

The most common renal anomaly was unilaterally non-visualized kidney in 15 out of the 40 patients (37.5%). The contralateral solitary kidney in 7 of these 15 patients was normal. Among the remaining 8 patients (8 renal units), 3 had



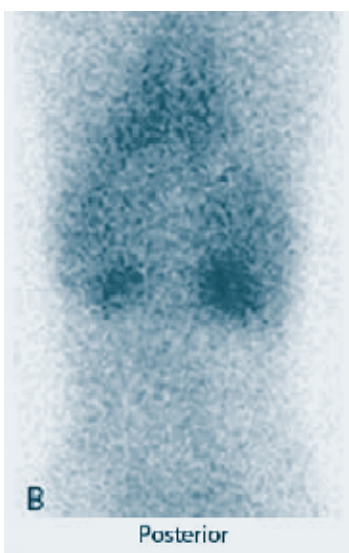


Figure 1. (A): Diuretic renal scintigraphy using ^{99m}Tc-DTPA. Left kidney shows good perfusion and cortical tracer uptake followed by unobstructed drainage. (B): ^{99m}Tc-DMSA renal cortical scintigraphy reveals grossly increased background tracer activity. Severely impaired tracer uptake by both kidneys is noted suggesting bilateral severely impaired renal function.

Table 1. *The imaging performed in every patient and their results. Data on MCUG were not available for all the patients*

Patient	Age (months)	Sex	DTPA / EC	DMSA	Repeat study	Left Kidney	Right Kidney	USG
1	1.5	M	Yes	No	No	RRF <30%	HDN, IFK	HDN, SK
2	3.5	M	Yes	No	No	Normal	Normal	HDN
3	1	M	Yes	No	Yes	HDN	HDN	HDN
4	1.5	M	Yes	No	No	Scar, RRF <30%	NFK	NVK
5	24	M	Yes	No	No	Normal	NFK	HDN
6	13	M	Yes	No	No	HSK, HDN	HDN, HSK	? HSK
7	1	M	Yes	No	No	Normal	Normal	HDN
8	35	M	Yes	No	No	HDN, UPJO	Normal	UPJO
9	1.5	M	Yes	No	Yes	HDN	HDN	HDN
10	1.5	M	Yes	Yes	Yes	NFK	HDN	NVK
11	1.5	M	Yes	No	No	PFK	PFK	SK
12	6	M	Yes	No	No	Normal	Normal	HDN
13	2	M	Yes	No	No	Normal	NFK	NVK
14	120	M	Yes	No	No	Normal	NFK	SK
15	72	F	Yes	No	Yes	RRF <30%	IFK	SK
16	1.5	M	Yes	Yes	No	Normal	Normal	HDN
17	132	F	No	Yes	No	IFK	IFK, HDN	SK, HDN
18	3	M	No	Yes	No	Normal	NFK	NVK
19	72	M	Yes	Yes	No	RRF <30%, HDN	PFK	NVK
20	72	M	No	Yes	No	Normal	NFK	NVK
21	60	M	No	Yes	No	APN / Scar, RRF <30%	NFK	NVK
22	60	M	Yes	Yes	No	Small kidney	Normal	SK
23	1.5	M	No	Yes	No	NFK	Ectopic	Ectopic
24	7	M	Yes	Yes	No	RRF<30%,	PFK	SK
25	5	M	Yes	Yes	No	Ectopic	NFK	Ectopic
26	2	M	Yes	Yes	Yes	HDN, UPJO	Normal	HDN
27	250	M	No	Yes	No	Normal	Scar, RRF<30%	HDN
28	1	M	Yes	No	No	NFK	HDN	HDN
29	2	M	Yes	No	No	Normal	NFK	SK
30	7	M	Yes	No	No	NFK	RRF<30%, APN	SK
31	2	M	Yes	Yes	No	Normal	Normal	HDN
32	0.5	M	Yes	No	No	HDN	NFK	HDN
33	4	M	Yes	Yes	No	Normal	Normal	HDN
34	3	M	Yes	Yes	No	Normal	NFK	NVK
35	6	M	Yes	Yes	Yes	Normal	Normal	HDN
36	15	M	Yes	Yes	Yes	Scar	Normal	HDUN
37	9	M	Yes	No	Yes	Normal	Normal	HDN
38	15	M	Yes	Yes	Yes	Normal	Scar	HDUN
39	3	M	Yes	Yes	Yes	Scar	Normal	HDUN
40	9	M	Yes	No	Yes	Normal	HDN	HDN

NVK- Non-visualised kidney, PFK- Poorly functioning kidney, IFK – Mildly impaired function of the kidney, HDN – Hydronephrosis, APN – Acute pyelonephritis, HSK- Horse shoe kidney, SK – Small kidney, HDUN – Hydro-ureteronephrosis, NFK – Non-functioning kidney, UPJO – Ureteropelvic junction obstruction

hydronephrotic changes in the visualized kidney without obstructed drainage, 3 had pyelonephritic changes/scars, and 2 had an ectopic functioning kidney. Figure 2 represents the abnormalities in these 15 patients. The second most common abnormality was hydronephrosis (HDN). It was identified in 12 of the 40 patients and included 1 patient with hydroureteronephrosis. Two patients had pelviureteric obstruction confirmed and treated surgically. One patient had a horseshoe kidney with both moieties being hydronephrotic. The remaining 8 patients showed unobstructed renal drainage on scintigraphy and are being followed up with serial renograms.

Scarring/pyelonephritic changes were noted in 7 of the 40 patients (7 renal units). Four of these seven patients had severely damaged kidney with relative renal function of less than 30% indicating significant renal function impairment. Of the 65 functional kidney units, 7 had relative renal function of less than 30%. Four of these 7 had also scars. In the other 3 patients, the reason for having mall kidneys could not be ascertained. Five patients had severely compromised renal function bilaterally and had progressed to chronic renal failure during the study. Table 2 shows the tests performed in our patients and their findings.

Considering non obstructive HDN as benign, 12 patients (including solitary ectopic and horseshoe kidneys) were kept on follow-up for a median of one year (9 to 15 months) without any active intervention. These patients are still at risk for developing renal impairment, due to glomerular hyperfiltration. Fifteen patients had a significant abnormality like pelvicureteric junction obstruction, scarring or pyelonephritic changes in either of their kidneys, which could potentially impaired renal function. Figures 3 and 4 represent the scintigraphic findings of individual renal units and in patients at high risk, respectively.

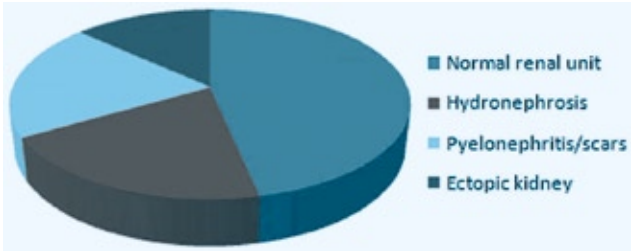


Figure 2. Pie chart showing scintigraphic findings in 15 patients with solitary functioning kidney. Seven of the 15 visualized renal units were normal. The remaining 8 had various abnormalities.

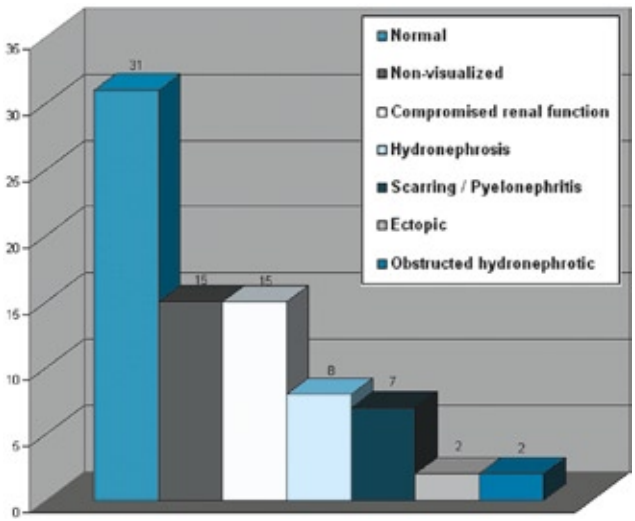


Figure 3. Profile of scintigraphic findings in individual renal units in patients with high ARM.

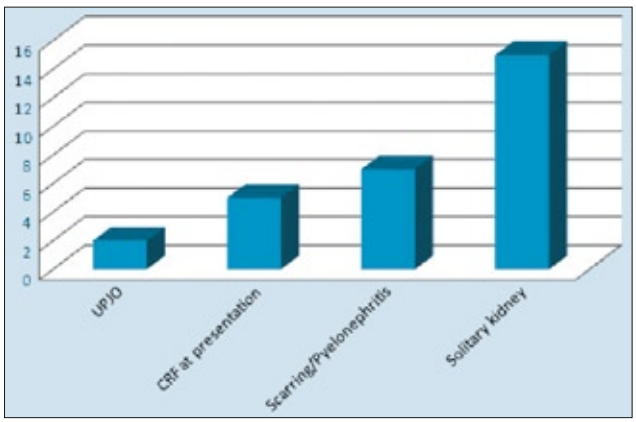


Figure 4. Bar chart showing scintigraphic findings in patients at high risk of severe renal damage. UPJO: uretero-pelvic junction obstruction. CRF: chronic renal failure.

Discussion

Of all the anomalies that co-exist with ARM, renal anomalies are the most frequent [8]. The incidence of anomalies varies from 25% to 60% in all cases of ARM [3-8]. Renal anomalies are less frequent in patients with low ARM but may be present in up to 60% in high ARM [9, 11]. Renal failure is the most common cause of morbidity and mortality in these patients [10]. Urologic abnormalities are rarely suspected clinically and require complete workup for their detection. The reported incidence of urologic abnormalities associated with high ARM varies from 30%-85% [11-16]. Eighty percent of our study population (61% of renal units) had a structural or functional abnormality of their urinary system. This high incidence may be due to the presence of high anorectal anomaly in all our patients. Ureteral injury during reparative surgery may be another rare reason. Some authors have noticed that boys are more likely to be affected with ARM than girls [17]. All but 2 of our patients were boys.

Table 2. *Shows the spectrum of abnormalities of the urologic system noted in patients with high ARM. Some patients had more than one abnormality*

S. No.	Abnormality	Number of patients
1	Solitary kidney	15
2	Hydronephrotic changes	11
3	Normal kidney	8
4	Scar/Pyelonephritis	7
5	Chronic renal failure	5
6	Pelvico-ureteric junction obstruction	2
7	Ectopic kidney	2

A non-visualized kidney was a common urological abnormality in our patients (37.5%) that may be attributed to renal agenesis or dysplastic non-functional kidney. Renal dysplasia is well known in patients with ARM. Ureteric bud, a part of the embryological collecting system, arises in response to adjacent metanephric mesenchyme. Ureteric bud formation is initiated at about five weeks of gestation and failure of ureteric bud outgrowth results in renal agenesis [18]. The position of the ureteric bud relative to the metanephric mesenchyme is also critical in renal development [18]. Ectopic positioning results in abnormal ureteric bud-metanephric mesenchymal interactions and is associated with renal dysplasia. Ectopic positioning of the ureteric bud is also thought to contribute to the integrity of the ureterovesical junction and an abnormal position of the ureteral orifice in the bladder was associated with vesicoureteral reflux in humans [19]. The complex embryological abnormality in these patients could have also involved the ureteric bud.

Some children and many adults with unilateral renal agenesis or hereditary disorder in a solitary functioning kidney develop proteinuria and reduced renal function [20, 21]. Patients with a solitary functioning kidney are also at increased risk of developing future chronic renal disease. The solitary kidney undergoes compensatory hypertrophy. There is glomerular hyperfiltration rate (GFR) in the functioning kidney, which gradually progresses to glomerular sclerosis and renal dysfunction [22, 23]. This has been confirmed in animal studies [24-26].

The most common urologic abnormality in patients with ARM is HDN. Some studies have shown vesico-ureteric reflux (VUR) to be one of the most frequent findings associated with

ARM [16, 27, 28]. In our study, HDN and VUR are among the most frequent findings. Hydronephrosis was present in 28% of our patients. In 5 patients with history of repeated episodes of UTI, MCUG detected VUR. However, the actual incidence of VUR as the cause of HDN could not be assessed as MCUG was not performed in all patients. Other minor anomalies in our study group included renal ectopia and pelvic ureteric obstruction. A fraction of the patients also showed pyelonephritic changes/scars on ^{99m}Tc-DMSA scinitigraphy probably related to vesico-ureteric reflux.

A recent study by showed that only 2 of the 84 patients treated surgically developed chronic renal failure [29]. The main difference of this study from our study was that only 25% of their patients had high type anorectal malformations. In our study, 17% of the patients had a renal unit with relative function less than 30% at the time of investigation. Another 12% had bilaterally impaired renal function and were labeled as having chronic renal failure. This proportion is very high, considering that nearly 70% of our population comprised of children below 1 year of age. A significant percentage of the patients with other abnormalities like scar and solitary functioning kidney are at higher risk for worsening renal function. The mean age of the patients who had chronic renal failure was 41 months (range 1.5 months to 132 months). Solitary kidney was present in 37.5% of our population. Almost 50% of the children with solitary kidney had an abnormality in that kidney. Hence a majority of these patients are at high risk for progressing to end stage renal disease, unless proper evaluation and appropriate treatment is instituted.

USG is an important non-invasive method for evaluation of the urologic system. Hydronephrosis, small sized kidneys and thinning of renal parenchyma can point towards impairment of renal function. Ultrasound (USG) is mainly a morphologic imaging modality that provides little information about the functional status of the kidney. Moreover, the subjective nature of USG makes it a very cumbersome tool for follow-up.

Until recently, intravenous urography (IVU) was used to evaluate renal function. However, the procedure is difficult in younger babies as it requires adequate bowel preparation, delivers a relatively high radiation dose and has a theoretical risk of hypersensitivity reaction. In addition, iodinated contrast agents are contra-indicated in patients with elevated serum creatinine levels, and the function of compromised kidneys may be underestimated.

Diuretic renography offers distinct advantages in comparison to IVU. It is a highly sensitive investigation in the evaluation of renal function and can be safely used in infants to determine the significance of HDN. In patients with suspected renal agenesis or dysplasia, ^{99m}Tc-DMSA cortical scintigraphy is of immense utility to locate and identify the functioning cortex of an ectopic kidney. ^{99m}Tc-DMSA imaging may be considered a non-invasive first line investigation (prior to MCUG) in evaluating patients with VUR and UTI. Further invasive investigations like MCUG are to be performed if ^{99m}Tc-DMSA scans are abnormal. This is based on the finding that children with a negative ^{99m}Tc-DMSA renal scan during their first UTI episode rarely have VUR and may never have high-grade VUR [30]. Early ^{99m}Tc-DMSA renal scanning has been called the top-down approach, because the focus is the identification of kidney injury rather than reflux [31]. Once diagnosis of high ARM is established, other parameters like relative renal function, creatinine clearance and GFR may be used as baseline values, while following-up high risk patients.

The main limitation of this study is that this is a retrospective analysis of patients with high ARM referred for renal scintigraphy. All patients had USG abnormalities of the urinary tract, a potential source of referral bias that may have resulted in higher incidence of detected abnormalities. Details of MCUG data were not available in most of these patients making it impossible to identify the incidence of VUR. Scintigraphy alone will not be able to differentiate between a dysplastic kidney and non-functioning kidney due to other causes like VUR. If measures to prevent renal damage due to VUR were to be undertaken, the actual incidence of VUR in these patients would be necessary.

In conclusion, this study suggests that urologic anomalies in infants with high ARM may remain clinically silent and eventually lead to severe renal damage and chronic renal failure. Unilaterally non-visualised kidney and hydronephrosis were the most frequent abnormalities in this study**.** Urological anomalies are the most common cause of morbidity and mortality in ARN. Renal scintigraphy provides valuable information necessary for risk stratification and appropriate management of these patients.

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Small river outside Karitsa village SW of Larisa by Dr. Elisabeth Molyvda.