Renal Parenchyma Abnormalities in Infants With Dilating Vesicoureteral Reflux: Relation to Reflux Severity and Pressure at Onset

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Purpose: We used ^{99m}technetium dimercapto-succinic acid scans in infants to determine the relation between renal deformities and severity of primary dilating reflux. We also used videourodynamics to analyze the association between detrusor pressure at onset of reflux and degree of renal changes.

Materials and Methods: A total of 20 patients (15 males) 0.10 to 1.3 years old (median 0.75) with grade III to V reflux underwent conventional filling videourodynamics. ^{99m}Technetium dimercapto-succinic acid scans were done 6 months after the last febrile urinary tract infection (median age 0.58 years).

Results: Nine males and 1 female had bilateral refluxing ureters, and 10 patients had unilateral reflux (grade III in 10, IV in 11 and V in 9). Among the 30 refluxing ureters renal changes were present in 19 kidneys (63%). Prevalence of renal changes according to reflux grade III, IV and V was 40%, 63% and 89%, respectively ($p < 0.02$). Reflux occurred in 13 patients (21 ureters) with detrusor pressure less than 10 cm water and in 7 (9) at 30 to 70 cm water (median 39.5). Renal changes were significantly more common in low pressure, low volume refluxing ureters (84.6%) compared to ureters refluxing at higher volumes and low pressure (37.5%, $p < 0.02$). At higher pressure reflux renal deformities occurred in 55.5% of refluxing ureters (5 of 9). Five patients had renal function impairment (mean creatinine for age 0.92 mg/dl, range 0.60 to 1.53).

Conclusions: High grade reflux and reflux occurring in the first half of bladder filling at low pressure are risk factors for renal changes in this cohort of infants.

Key Words: infant, renal insufficiency, technetium Tc 99m dimercaptosuccinic acid, urodynamics, vesico-ureteral reflux

Abbreviations and Acronyms

^{99m}Tc = ^{99m}technetium
CBC = cystometric bladder capacity
DMSA = dimercapto-succinic acid
Pabd = intra-abdominal pressure
Pdet = detrusor pressure
Pves = intravesical pressure
RU = refluxing ureter
UTI = urinary tract infection
VUD = videourodynamic testing
VUR = vesicoureteral reflux

Submitted for publication October 9, 2009.

VESICOURETERAL reflux is a common condition found in pediatric urological practice. Reflux is generally detected by investigation of prenatal pyelocaliectasis, after a febrile urinary tract infection or in siblings of patients with reflux.[1]

Primary VUR results from congenital maldevelopment of the ureterovesical junction in the absence of bladder outlet obstruction or neurological disorders of the lower urinary tract. Other investigators have considered that primary reflux in infants may occur as a result of lower urinary tract dysfunction, which may induce VUR in a marginally competent ureterovesical junction.[2,3] VUR is clinically associated with acute pyelonephritis and kidney parenchymal changes (renal dysplasia, segmental hypoplasia or acquired scarring lesions), which may lead to renal function impairment or hypertension, or predispose to increased morbidity during pregnancy in females.[4–6] Some authors report

0022-5347/10/1836-2367/0
THE JOURNAL OF UROLOGY®

Vol. 183, 2367-2372, June 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2010.02.2386

bladder volume and Pves level at which reflux occurs as predictors of reflux outcome and its association with kidney changes.[7,8]

We sought to evaluate the association between primary dilating reflux and severity of renal parenchyma changes in infants using ^{99m}Tc DMSA. We also analyzed the relation between Pdet at onset of VUR and the degree of renal abnormalities for each refluxing renal unit determined by VUD.

MATERIALS AND METHODS

We retrospectively studied 5 female and 15 male infants with primary dilating VUR treated at our hospital between 1999 and 2007. Most of these patients were referred, at a median age of 0.16 years (range 0.02 to 0.50), by pediatricians who had diagnosed VUR by conventional voiding cystourethrography. Patients with VUR secondary to lower urinary tract malformations, bladder outlet obstruction, completely duplicated collecting system, ureteroceles or neuropathic bladder dysfunction were excluded. On hospital admission a medical history was done and low dose continuous antibiotic prophylaxis was started with either trimethropin (2 mg/kg daily) or first generation cephalosporin (20 mg/kg daily) in all cases. Febrile UTI was the initial presentation in 15 patients and 5 were evaluated for prenatal pyelocaliectasis. None of the male infants had been circumcised. All patients were further evaluated with VUD at a median age of 0.75 years (range 0.10 to 1.3) at least 2 to 3 weeks after the last UTI. Urine sterility was confirmed by urine culture analysis.

VUR was graded according to the International Reflux Study in Children and to maximum reflux grade recorded on VUD.[9] Assessment of renal parenchyma morphology and function involved urinary tract ultrasound and ^{99m}Tc DMSA scan. Renal scintigraphy was done not less than 6 months after the last febrile UTI, at a median age of 0.50 years (range 0.50 to 0.91). All infants received an intravenous dose of ^{99m}Tc DMSA adjusted to individual body surface area. Two to 4 hours after injection high resolution images of each kidney in a posterior and posterior oblique planar projection were obtained by high resolution gamma camera with the patient in the supine position.

Dysmorphic kidneys were categorized into 4 types on ^{99m}Tc DMSA scan, namely single focal cortical defect with uniform uptake by the rest of the kidney, more than 1 focal cortical defect, generalized poor isotope uptake and small contracted kidney with poor tracer uptake (fig. 1). Renal function assessment included measurement of serum creatinine by the enzymatic ultraviolet method, correlated with age.[10]

VUD was done using a standardized method described previously.[11,12] VUD included measurement of Pves and Pabd and subtracted pressures with synchronous fluoroscopic monitoring of the lower urinary tract. Fluid filled lines were used to transmit bladder and intrarectal pressures to external transducers placed at the level of the pubic symphysis. Contrast medium (iothalamase meglumine 17% solution) was introduced into the bladder by gravity from a height of 70 cm for 4 to 5 minutes of artificial filling at room temperature via a separate urethral catheter.

Maximum CBC was calculated as percent of mean expected bladder capacity for age using the formula, 30 $\times$ age (years) + 30.[13] End filling Pdet was determined after filling had stopped and pressure had remained at a stable level for several seconds. Voiding phase assessment comprised measurement of maximum voiding pressures when fluoroscopy image showed an open bladder outlet (bladder neck and urethra) as well as when the posterior urethra was dilated due to intermittent contractions of the urethra/periurethral sphincter.

Cystometric tracings with synchronous fluoroscopic images of the lower urinary tract were stored and reviewed on a high quality television monitor in real-time recording and frame by frame in slow playback motion. Attention was directed to Pdet values and estimated bladder capac-

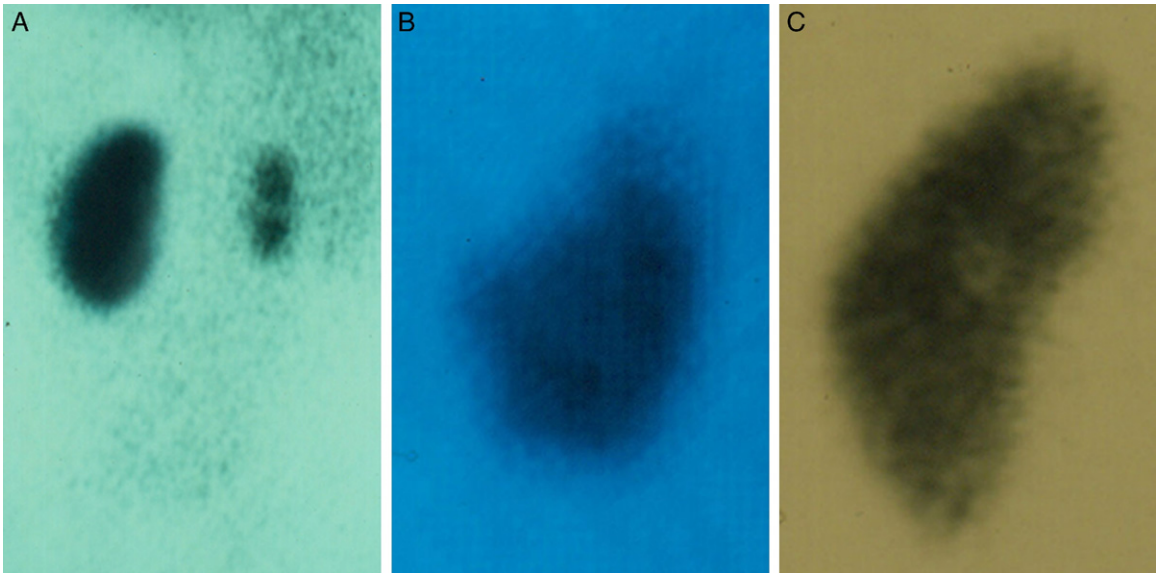

Figure 1. DMSA scan of renal status assessment. *a*, normal and small dysmorphic kidney. *b*, focal defect. *c*, generalized poor uptake.

ity (first and second half of filling phase) at which reflux occurred. Reflux occurring at high pressure during filling (phasic detrusor contractions) or throughout voiding was also included.

Chi-square test was used to compare renal changes according to VUR grade, Pdet values and bladder capacity at onset of reflux. Statistical significance was considered at $p < 0.05$.

RESULTS

Nine males and 1 female had bilateral VUR, and 10 patients had unilateral reflux. VUR was grade III in 10, IV in 11 and V in 9 ureters. A total of 24 refluxing renal units were observed in 15 males (bilateral in 9, unilateral in 6) and 6 refluxing renal units were seen in 5 females (bilateral in 1, unilateral in 4, table 1).

Among the 30 RUs renal abnormalities were found in 19 kidneys (63%), while 11 (37%) had an even isotope uptake. Two of the 19 dysmorphic kidneys (11%) had a single focal cortical defect (corresponding to reflux grade III in 1, grade IV in 1), 4 (21%) had more than 1 focal cortical defect (IV in 3, V in 1), 7 (37%) had a generalized decrease in tracer uptake (III in 2, IV in 2, V in 3) and 6 (32%) had a small dysmorphic kidney (III in 1, IV in 1, V in 4).

Comparison of renal abnormalities identified in 73% of males (11 of 15, 16 RUs) and 40% of females (2 of 5, 3 RUs) did not show statistical significance ($p = 0.29$). Conversely renal changes according to VUR grades III, IV and V were seen in 40%, 63% and 89% of patients, respectively ($p < 0.02$).

Eight patients (13 of 30 RUs) had initiation of VUR during early bladder filling without increase in Pdet (less than 10 cm water), 5 (8) had VUR at low Pdet in the second half of the storage phase and 7 (9) had reflux during voiding (median voiding pressure 39.5 cm water, range 30 to 52, table 2). In 1 of the latter 9 RUs unilateral reflux (grade III) was triggered by a phasic detrusor contraction of 70 cm water during filling. In this patient reflux disappeared as Pdet decreased, although during voiding reflux (grade III) occurred in the left ureter and reappeared in the right ureter.

Comparison of renal changes identified in 11 of 13 RUs (85%) refluxing at low pressure in the first half of the storage phase, 3 of 8 (38%) refluxing at low pressure in the second half of filling and 5 of 9 (56%) refluxing at higher pressures revealed no statistically significant differences ($p = 0.07$). When we compared renal changes in ureters refluxing during filling (67%) to those refluxing during voiding (56%) no significant differences were noted ($p = 0.56$). In contrast, renal deformities observed in RUs at low pressure during the first half of filling were statistically different compared to those noted in the second half of the storage phase ($p < 0.02$). At a mean followup of 6 months renal function impairment (median serum creatinine for age 0.64 mg/dl, range 0.50 to 1.70) was noted in 5 cases (table 3).

All but 1 patient had normal detrusor activity during filling (fig. 2). In all but 3 cases voiding alternated spikes of high pressure (median 92.5 cm water, range 51 to 125) concurrent with intermittent contractions of the urethra/periurethral sphincter mechanism, followed by coordinated voiding at normal pressures (39.5, 30 to 52). Peaks of isometric pressure quickly returned to normal levels with relaxation of the urethra/periurethral sphincter (fig. 3). One of these 3 patients had coordinated voiding without spikes in voiding Pdet. Two other patients had interrupted streams of urine during voiding due to unsustained detrusor contractions without abdominal straining. CBC of these latter patients was above normal for age and residual urine was greater than 30% of bladder capacity. CBC adjusted for age, expressed as percent of mean normal value, was less than 80% in 2 patients and greater than 150% in 8. Post-void residual urine greater than 30% of CBC for age was noted in 6 patients (table 4).

Table 1

Reflux Grade	No. Refluxing Units/Total No. Males (%)	No. Refluxing Units/Total No. Females (%)
III	7/24 (29)	3/6 (50)
IV	8/24 (33)	3/6 (50)
V	9/24 (38)	0/6 (0)

Table 2

	No. Refluxing Units/Total No. (%)	No. Kidney Damage/ Total No. (%)
No. at filling:		
First half	13/30 (43)	11/13 (85)
Second half	8/30 (27)	3/8 (38)
No. at voiding	9/30 (30)	5/9 (56)

DISCUSSION

This study recorded the incidence of irreversible renal parenchyma abnormalities using ^{99m}Tc DMSA scans for infants and kidneys affected with reflux, as well as Pdet at the onset of reflux. We identified

Table 3

Mean Age at Evaluation (yrs)	VUR Grade (rt/lt)	Serum Creatinine (mg/dl)*
0.6	IV/IV	0.50
0.6	IV/IV	0.64
0.4	V/V	1.70
1.4	III/III	1.22
0.6	V/V	0.60

All patients in this analysis were male and all had bilateral reflux on DMSA scan.
* Normal 0.2 to 0.4 mg/dl at age 1 to 12 months, 0.2 to 0.7 mg/dl at age 1 to 3 years.

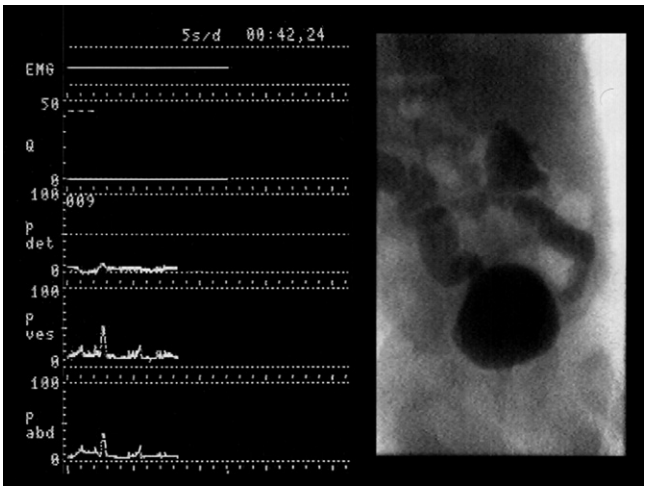

Figure 2. VUD static frame of storage phase in 3-month-old male. Note 3 pressure tracings and normal detrusor activity during filling. Synchronous fluoroscopic image shows smooth walled bladder with bilateral dilating reflux during first half of filling. Pdet counter indicates 9 cm water.

bilateral reflux in 9 males and 1 female at a median age of 0.75 years. VUR was mainly diagnosed after a febrile UTI and in a small group after prenatal diagnosis of pyelocaliectasis.

Abnormal ^{99m}Tc DMSA scans increased significantly with severity of VUR grade for each renal unit. Renal abnormalities were noted in 19 of 30 refluxing kidneys (63%), corresponding to 11 males and 2 females. Generalized parenchymal changes and small retracted kidneys were more frequently noted than focal cortical defects. Renal scans were done 6 months after the last documented febrile UTI to avoid transient scan defects, which can persist for 2 to 4 months after acute pyelonephritis.[14,15] Limitations of renal scans include differential diagnosis between congenital renal lesions and acquired damage in dysmorphic kidneys associated with VUR.[7,15]

Table 4

	Median (range)
CBC (ml)	72.5 (20–180)
% Normal capacity	1.45 (0.4–4.80)
End filling pressure (cm water)	5 (2–15)
Voiding pressure (cm water):	
Open bladder outlet	39.5 (30–52)
Sphincter overactivity	92.5 (51–125)

Six patients had residual urine (greater than 30% capacity). One patient only had detrusor instability.

Anderson and Rickwood reported that in 34 infants (91% males) with 55 primary RUs detected by prenatal ultrasound 60% of renal abnormalities were associated with reflux grade III to V.[16] They found, as we did, a high incidence of kidneys with generalized decreased isotope uptake or kidneys with virtual nonfunction associated with dilated VUR. Yeung et al also reported the relation among gender, kidney damage and severity of VUR in 155 infants with primary reflux.[17] Recently Sjostrom et al noted that 85% of infants with VUR had renal changes at hospital admission.[18]

We used VUD to examine the relation between Pdet at which reflux occurred and the severity of renal parenchyma changes in infants with reflux. Recordings of VUD were stored, reviewed, reversed and stopped for analysis at any point. Interestingly detrusor activity was normal during filling in 19 patients, except in 1 who had a phasic detrusor contraction that induced unilateral reflux grade III, which subsided when the detrusor contraction ceased. We detected by slow motion playback of VUD that during bladder emptying in all but 3 patients intermittent contractions of the urethra/periurethral sphinter caused peaks of isometric pressure followed by normal urethral function, defined as an open and relaxed bladder outlet that permitted voiding at normal pressure. More

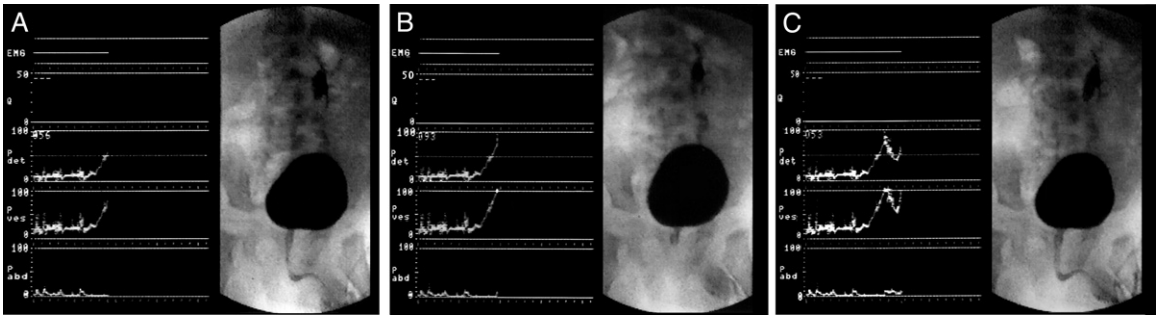

Figure 3. Three static frames of voiding phase in 8-month-old male with unilateral VUR reveal effect of sudden contractions of distal sphincter mechanism on urethral lumen. Flowmetry and electromyogram tracks are turned off. *a*, oblique fluoroscopic view of lower urinary tract. Note open bladder neck and well delineated urethra. Reflux occurs at voiding pressure of 55 cm water. *b*, urethral lumen is occluded by action of distal sphincter contraction associated with high peak of isometric Pdet of 93 cm water. Reflux grade remains unchanged. *c*, fluoroscopic image demonstrates recovery of normal urethral configuration. Pdet counter indicates 53 cm water. Reflux grade again remains unaltered.

importantly these spikes of isometric Pdet did not cause or initiate reflux in any of our patients except the patient mentioned previously who had a phasic detrusor contraction during filling. One of the 3 patients had an entire coordinated voiding phase and 2 emptied the bladder in several small voiding volumes due to unsustained detrusor contractions. These observations are similar to those we reported previously in infants with and without reflux.[12]

Yeung et al used physiological filling cystometry to study 42 infants with primary reflux, noting that 7 (17%) demonstrated dyscoordinated voiding with good bladder emptying and 10 (24%) had exaggerated interrupted voiding with inadequate bladder emptying.[2] Likewise, Sillen et al used noninvasive 4-hour voiding records and observed interrupted voiding in 12 of 33 males with reflux (36%).[3] They reported a lower incidence of interrupted voiding in healthy infants without reflux compared to those with reflux.[2,3]

Differences in cystometric findings between the reports cited and our study may be explained by variations in the methodology used to assess lower urinary tract behavior, ie noninvasive techniques (frequency/volume diary) vs invasive urodynamic testing, or by the effect of performing cystometrogram with different bladder filling rates (faster filling vs physiological filling), which influences resulting measurements.

In our series there were 13 patients (21 RUs) with reflux at Pdet less than 10 cm water but only 7 (9) at 30 to 70 cm water. Of the 21 RUs at low pressure 13 initiated reflux at small bladder volumes, compared to 8 at larger bladder capacities. Renal abnormalities were statistically more frequent in patients who had reflux early during filling at low pressure (85%) than in those who had reflux at low pressure in the second half of the storage phase (38%). Limitations of this study are related to the small number of cases.

More than 40 years ago Lattimer et al indicated that reflux occurring with small bladder volumes and low pressure was associated with increased renal damage, whereas ureters refluxing at higher pressure had lower degrees of renal damage.[8] These conclusions are similar to our findings. McLaren and Simpson studied 82 patients younger than 1 year with reflux using radionuclide cystogram to grade reflux, and renal scintigraphy to assess renal lesions.[19] They also concluded that reflux occurring at low bladder volume was frequently associated with kidney lesions compared to renal units refluxing at moderate or high bladder volumes. More recently Godley et al reported that during filling reflux volumes increased progressively with low pressures or with an abnormal increase in bladder pressure but only 1 of 11 patients had initiation of reflux during voiding.[20] Furthermore, reflux initiated during filling and observed during voiding did not increase with peaks of detrusor voiding pressure.

CONCLUSIONS

We found an association between dilated reflux occurring early during filling without Pdet increase and renal abnormalities. Dilating reflux and reflux present at low pressure and low bladder capacities are risk factors for renal damage in infants.

ACKNOWLEDGMENTS

M. L. Calcagno provided advice on statistical analysis. Roque Puleio and Santiago Gonzalez from CONICET (National Research Council) performed the videourodynamic studies.

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EDITORIAL COMMENT

Despite the small number of patients, the authors present an interesting study of the urodynamic parameters under which high grade primary reflux occurs, the incidence of renal scarring and the role bladder dynamics may have in subsequent renal injury in otherwise normal infants. However, while the authors report detrusor pressures at the onset of reflux, it is important to distinguish that these pressures were measured at urodynamic evaluation and not necessarily when reflux originally occurred. The DMSA scans documenting renal scarring were performed 6 months after the last febrile UTI, which is presumably when the renal insult occurred.

As the median patient age at scanning was 0.5 year, the reflux driving the process was likely present in the first month of life. The urodynamic evaluations were performed at a median patient age of 0.75 year or approximately 8 to 9 months later. This is not to say that the authors are incorrect in reporting that most reflux occurred at low pressure in these patients, only that one should be cautious when retrofitting the urodynamic findings at that time to what was occurring when the insult initially took place. Detrusor hyperactivity and intermittent external sphincter activity during voiding resulting in transiently increased detrusor pressures are common in early infancy, tend to lessen over time and conceivably could have had a more prominent role in these patients.

The conclusion that reflux at low pressure is a risk factor for renal scarring is somewhat of an overstatement. The majority of infants with or without reflux have low pressure storage of urine and, in the absence of external urethral sphincter activity, normal voiding pressures. The authors provide valuable documentation that most primary VUR is present in a low pressure milieu and reconfirm that male gender, bilaterality and the presence of grade V VUR have strong associations with more severe renal scarring and ultimately impaired function.

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