Greater reliability of neonatal ultrasonography in defining renal hypoplasia with antenatal hydronephrosis and vesicoureteral reflux

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Purpose: *Infants with history of antenatal hydronephrosis and neonatal vesicoureteral reflux may have detectable changes in renal scans before the advent of urinary tract infection. In cases of bilateral high-grade vesicoureteral reflux, differential renal function on renal scan may not reveal renal hypoplasia since comparison of relative function may be made between two abnormal kidneys. We tested the hypothesis that ultrasonography in the neonatal period may be accurate and complementary to renal scan in detecting renal hypoplasia at birth.*

Materials and methods: *Twenty-six infants who presented in the antenatal period with history of hydronephrosis and were noted to have neonatal vesicoureteral reflux postnatally were studied retrospectively. They had all been treated by a prospective protocol that included renal ultrasound and renal scans in the first 6 weeks of life. All had been placed on prophylactic antibiotics and had no urinary tract infection. Multiple sonographic parameters were analyzed including kidney length, echogenicity, calyceal blunting, parenchymal thinning and focal scars. We correlated the renal morphology on ultrasound, the renal function on renal scan and the degree of reflux seen on VCUG.*

Results: *VCUG showed reflux in 44 renal units, grade of reflux was: I (2), II (7), III (12), IV (8), and V (15). A variety of nucleides were used including DMSA in 15, DTPA in 6 and MAGIII in 5. Renal scans identified global hypoplasia without focal scars (differential function less than 40%) in 10 of 44 refluxing renal units grades I (1), III (2), IV (4), and V (3). The sonographic finding of decreased renal length (<50th percentile for age) was present in 14 refluxing units of 44 refluxing renal units, grade I (1), grade III (4 bilaterally in 1), grade IV (4 bilaterally in 1), and grade V (5 bilaterally in 2). The sonographic finding of decreased renal length (<50th percentile) correlated strongly with renal hypoplasia on renal scans in refluxing renal units (p value < .005, sensitivity 80% and specificity 82%, positive predictive value 57%, and negative predictive value 93%).*

Conclusion: *Postnatal ultrasonography is a reliable measure of gross renal parenchyma, and in the presence of vesicoureteral reflux correlates with renal scintilligraphy. In addition, for cases of bilateral neonatal vesicoureteral reflux, ultrasound and renal scan are complimentary, each being able to detect the abnormalities that might be missed by the other.*

Key Words: neonatal vesicoureteral reflux, ultrasonography, renal hypoplasia, renal scan

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Introduction

With the introduction of prenatal ultrasound, approximately 1% of fetuses have hydronephrosis.[1-3] Of these 10% to 15% may have neonatal vesicoureteral reflux.[1,4] Most of these patients are males (80%) and have bilateral high-grade reflux (III, IV, and V: 80%).[4-11] Over

the last decade, using differential renal function on the scans as the primary measure of defining renal injury debate has focused on the severity and prevalence of congenital renal injury on renal scans associated with neonatal vesicoureteral reflux.[7,9,11-14] However, in those children in whom the primary disease process is bilateral, as is seen in these infants, the differential function measure lacks a true control. We hypothesize that evidence of preexistent congenital renal hypoplasia although uncommon, may be detected by ultrasonography in the neonatal period, and that renal ultrasound may be complementary to renal scan in providing clinical information for bilateral high grade reflux.

Materials and methods

Between January 1993 and December 1998, 260 patients diagnosed with antenatal were hydronephrosis seen in the neonatal period. All patients were treated in a prospective fashion with a protocol that included antibiotic prophylaxis (Trimethoprin 2mg/kg/day) and then evaluated with abdominal and pelvic ultrasound in the first week of life, followed by a voiding cystourethrogram. Only infants with primary reflux (e.g. no posterior urethral valve, duplication, or ureterocele) were included in this analysis. Reflux was graded according to the International Classification of Reflux[15] and hydronephrosis was graded according to the SFU (Society of Fetal Urology).[16] In this study we correlated the renal morphology as seen on ultrasound with the renal function on renal scan and the degree of reflux seen on VCUG.

Ultrasound was performed with a real time ultrasound scanner and a 5MHz convex transducer. Bladder, kidneys, and adrenals were scanned with the babies supine. The kidneys were scanned from the back to measure renal dimensions. Attempts to precisely measure the length of kidneys was done in all patients and renal length less than 50th percentile for age was defined as abnormal, the nomogram (Figure 1) used was adapted from Han et al.[17] Other criteria included in the assessment were presence of hydronephrosis, blunting of calyceal system, parenchymal thickness, cystic changes, ureteral dilatation, and finally bladder wall thickness. Radionucleides utilized in the isotope imaging included DMSA, DTPA, or MAGIII, and these studies were done at approximately 1 to 2 months of age. One radiologist reviewed all renal nuclear scans; a pediatric urologist (GM) independently reviewed the corresponding renal ultrasounds.

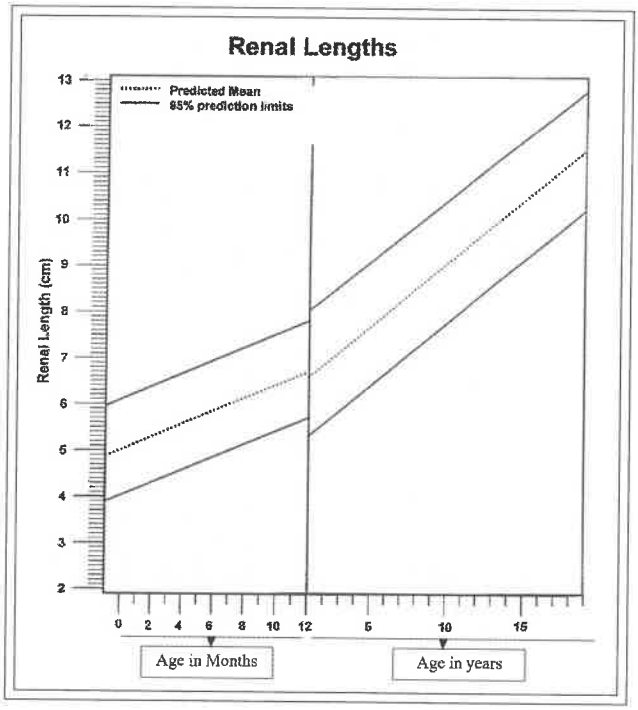

Figure 1. Renal size nomogram adopted from Han et al (with permission)

Results

Twenty-six infants with history of antenatal hydronephrosis and neonatal vesicoureteral reflux proven postnatally had ultrasound examinations (average age 5 weeks, range 4-8 weeks) and renal scans (average age 7 weeks, range 6-9 weeks) before the advent of urinary tract infections. Reflux was present in 44 renal units (19 males and 7 females). The grade of reflux in the 44 renal units was I (2), II (7), III (12), IV (8), and V (15). Reflux was bilateral in 15 males, and 3 females (Figure 2).

Renal scintilligraphy was done in all, and included DMSA in 15, DTPA in 6 and MAGIII in 5.

Renal scans identified global hypoplasia without focal scars (differential function less than 40%) in 10 of the 44 refluxing renal units (22%), and 2 non refluxing renal units (Table 1), for the refluxing renal units the corresponding grade of reflux was as follows: grade I (1), III (2), IV (4), and V (3).

The sonographic finding of decreased renal length (<50th percentile for age) was present in 14 refluxing units (27%) and 1 non refluxing unit (Table 1). Reflux was bilateral in 4 patients (8 renal units): bilateral grade III in 1, bilateral grade IV in 1, and bilateral grade V in 2. Unilateral vesicoureteral reflux was present in the other 6 renal units: grade I in 1, grade

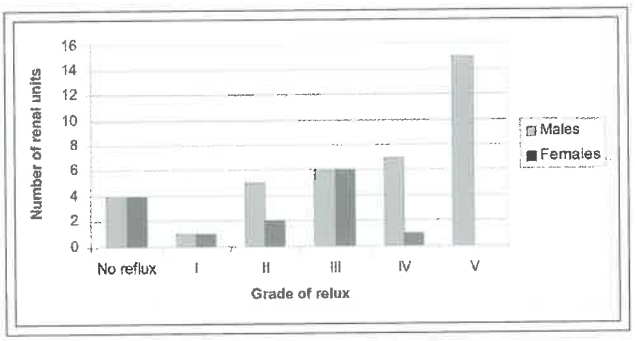

Figure 2. Reflux distribution between males and females.

III in 2, grade IV 2, and grade V in 1. Out of these 14 renal units, 8 had global atrophy on renal scan, while 6 of the remaining 32 refluxing renal units had only decreased renal length (p value < .005, sensitivity 80% and specificity 82%, positive predictive value 57%, and negative predictive value 93%).

Upon evaluating the differential renal function in the 6 refluxing renal units that had less than 50th percentile length and normal differential renal function, 4 of these renal units were present in patients with high grade bilateral reflux (2 patients). Whereby 1 renal unit is functioning less than 40%, hence allowing the conralateral renal unit relative function to remain normal. The remaining 2 renal units were present in one patient with bilateral grade V reflux and normal split renal function on renal scan (Figure 3).

Distribution of differential renal functions on renal scan and ultrasound findings for the refluxing and non refluxing renal units are shown in Table 1.

Hydronephrosis was present in 26 refluxing renal units (50%). The grade of hydronephrosis was as follows: grade I (4), II (12), III (4), IV (8); out of these 26 renal units only 7 had decrease renal function on renal scan. The grade of reflux in those 7 renal units was III (2), IV (3), and V (2).

Blunting of the calyceal system was found in 6 refluxing renal units (23%). Three of these 6 renal units had decrease function on renal scan. The grade of reflux was III (1), IV (1), and V (1).

Four kidneys showed severe thinning of the parenchyma compared to the contralateral kidneys, all 4 renal units had decrease renal function on renal scan. The grade of reflux was III (1), IV (2), and V (1).

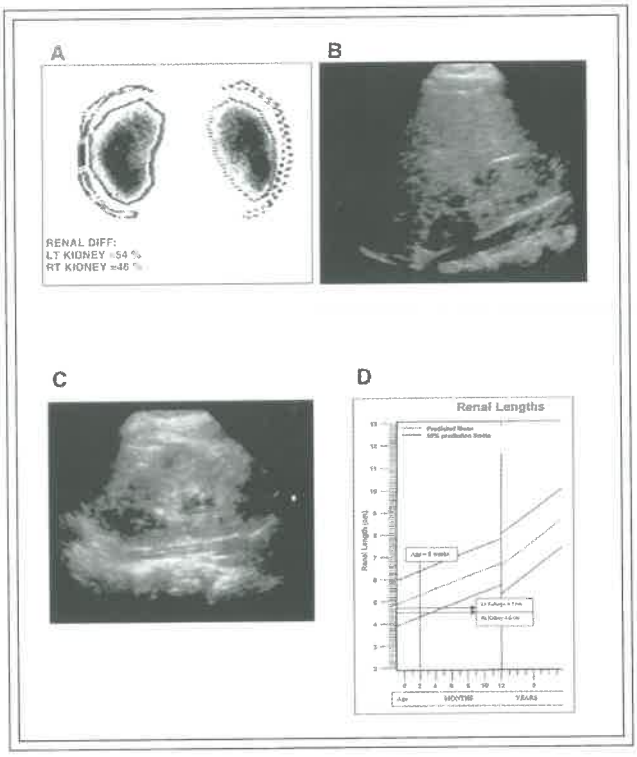

Figure 3. Patient with bilateral grade V vesicoureteral reflux and normal split function on renal scan.
A. Posterior views of right and left kidney reveals pattern of DMSA renal scan: split function 44% and 56% respectively.
B and C. Ultrasound images for the Right and Left kidneys.
D. Plotted renal lengths for both kidneys <50th percentile for age.

One ultrasound showed bilateral ureteral dilatation in bilateral grade V refluxing units (both kidneys had normal renal scan uptakes), and one patient had trabeculated bladder with no evidence of urethral pathology such as posterior urethral valves, the patient had bilateral grade V refluxing renal units,

TABLE 1. **Distribution of differential renal function and renal lengths between refluxing and non refluxing renal unit**

Number of renal units	Decreased renal Function (<40%)	Renal function (>40%)	Renal length (<50th percentile)	Renal length (>50th for age)
Refluxing renal units	10	34	14	30
Non refluxing renal units	2	6	1	7
Total	12	40	15	37

and global scarring on one side.

One kidney had multicystic and dysplastic changes on ultrasound, this renal unit had no vesicoureteral reflux and no function on renal scan (non-refluxing renal unit with < 40% renal function and renal length < 50th percentile for age). Focal renal scars were not accurately detected on either renal scan or ultrasound.

Discussion

Renal parenchymal impairment in association with ureteral reflux has been identified as one of the major cause of renal failure since Bailey and Hodson first described it.[18-20] Relative loss of renal function may be apparent in children with high-grade vesicoureteral reflux even in the absence of urinary tract infection.[13,21] Hiraoka et al[22] showed that all patients with congenitally small kidneys and reduced DMSA uptake were associated with ureteral reflux. The patterns of dimercaptosuccinic acid distribution associated with vesicoureteral reflux include polar defects, a medial defects, and small renal size and decreased renal length (global decreased uptake). The latter type is more likely to be due to congenital dysplasia than urinary tract infection while focal defects represent acquired scarring secondary to urinary tract infections.[23-26]

In particular, the appearance on scintigraphy (Dimercaptosuccinic acid renal scan) of the renal impairment in neonatal reflux is commonly characterized by global parenchymal loss with or without focal scarring.[10,11,13,21,22,27] Nguyen et al[27] evaluated the characteristics of renal abnormalities using DMSA in infants with neonatal reflux and no history of urinary tract infection, and noted that isolated cortical defects occurred in 7 out of 24 renal units. Although the authors attempted to determine the incidence of renal abnormalities before urinary tract infection, it is possible that infection may have been missed in some cases. In our study, we were not able to identify focal renal scars with either imaging modality, and we speculate that the use of different nucleides than DMSA (15/26 patients) may have limited our ability to identify focal scars in absence of global hypoplasia.

On the other hand, debate continues on whether the congenital reflux-related renal impairment is secondary to disordered embryogenesis, to "waterhammer" insult to the developing kidney, or as a result of superimposed urinary tract infection later in life.[7,9,11-14,27,28] We believe our data refute the possibility that infection was the cause of the renal scarring, since the infants were all on prophylatic antibiotics and had no clinical evidence of urinary tract infection or sepsis prior to either the ultrasound or renal scan. We can not draw any conclusion about potential "waterhammer" effect that may have occurred in utero.

Although most of the congenital reflux nephropathy have overall decreased renal radionuclide uptake, there is a major factor limiting the reliability of this study since the analysis of differential renal function relies on comparing isotope uptake in one kidney with another. In neonatal vesicoureteral reflux, a bilateral disease usually predominates in 80% of the cases and relying solely on renal scan uptake may well be misleading. Nguyen and colleagues[27] noted that in infants with bilateral reflux, renal hypoplasia was more likely to be unilateral although reflux grade was similar on both side, and the authors speculated that these findings may be secondary to sterile vesicoureteral reflux pressure toward one kidney than toward the other. In our study, we had the same observation whereby three patients with bilateral vesicoureteral reflux (III-V) had small kidney lengths, yet the renal scan was able to detect decreased uptake only on one side. In addition one patient with bilateral high-grade reflux and small kidneys on ultrasound had normal split renal function on renal scan. Although bilateral renal hypoplasia may be assciated with elevated serum creatinine, this was not the case in any of the patients. Whether this finding does have any impact on the clinical course of the disease is unknown and further follow up is needed.

Yeung et al[11] reported that the majority of kidneys exposed to grade I-IV vesicoureteral reflux show normal or near normal differential function and morphology on postnatal DMSA, and severe congenital renal damage is seen predominantly in association with vesicoureteral reflux grade V in males. In our series, the majority of refluxing units had normal function (> 40%), however we did see global hypoplasia with decreased function on renal scans (< 40%) in 20% of the renal units with grade III, IV and V. On the other hand, decreased renal lengths for age was found in 32% of the refluxing renal units (grade III, IV, and V). Of interest was the finding of bilateral small kidney in three patients with grade III-V reflux. This finding may reflect the outcome of disordered embryogenesis of the ureteral bud hypothesis,[29] and that the generalized renal damage may be a manifestation of growth arrest possibly due to glomerular damage secondary to a mismatch between a laterally positioned ureteral bud and the renal blastema during early gestation.[30] Hinchliffe et

al[31] reviewed 86 nephrectomy specimens histologically from patients with vesicoureteral reflux (with or without ureterovesical obstruction) to investigate the relationship between coexisting hypoplasia and postnatally acquired cortical damage. Hypoplasia was assessed independently of the acquired cortical loss using medullary ray glomerular counting. Severe hypoplasia, defined as 25% of normal was detected in 47 of 86 patients. The findings suggest a strong association of hypoplasia and vesicoureteral reflux. This data confirms that early postnatal presentation with minimal renal function need not necessarily reflect a failure of management but rather a pre-existing limitation of renal capacity and the sensitivity of 99 mTc-DMSA may reveal the permanent nature of the renal damage.

Postnatal ultrasonography is a reliable measure of renal parenchyma and correlates well with renal scintilligraphy. Particularly in bilateral high grade reflux because differential renal function on renal scan may not reveal renal hypoplasia since comparison of relative function may be made between two abnormal kidneys, the renal length on ultrasonography may be an objective criterion to initially assess renal capacity and for further follow up. In such patients where kidney sizes are small for age, renal scans may be used more selectively for the investigation during or after urinary tract infection. □

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