Longitudinal Development of Renal Damage and Renal Function in Infants With High Grade Vesicoureteral Reflux

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Purpose: We sought to study renal abnormality and renal function through time in infants with high grade vesicoureteral reflux.

Materials and Methods: This prospective observational study included 115 infants (80 boys and 35 girls) younger than 1 year with grade III to V vesicoureteral reflux. The diagnosis was made after prenatal ultrasound in 26% of the patients and after urinary tract infection in 71%. Patients were followed by renal scintigraphy, 51chromium edetic acid clearance and video cystometry. Median followup was 62 months.

Results: Renal abnormality, which was found in 90% of the children at followup, was generalized in 71% and focal in 29%. The abnormality was bilateral in 28% of the affected patients. Total glomerular filtration rate was less than 80% of expected in 30% of the patients. Single kidney function was less than 40% of expected total glomerular filtration rate in 71% of the patients. Renal status (parenchymal abnormality and function) remained unchanged through time in 84 of 108 available cases (78%), improved in 5 (5%) and deteriorated in 19 (18%). Predictive factors for deterioration were recurrent febrile urinary tract infection, bilateral abnormality and reduced total glomerular filtration rate. Deteriorated renal status was more common in cases diagnosed prenatally than in those detected after urinary tract infection.

Conclusions: Among these infants with high grade vesicoureteral reflux renal abnormality was frequent and was associated with subnormal filtration of one of the kidneys. Decreased total glomerular filtration rate was seen in about a third of the patients. Overall deterioration of renal status was seen in only a fifth of the patients. Infection control seems to be an important factor to minimize the risk.

Key Words: infant; kidney function tests; renal insufficiency, chronic; vesico-ureteral reflux

Abbreviations and Acronyms

51Cr EDTA = 51chromium edetic acid
CKD = chronic kidney disease
DMSA = dimercapto-succinic acid
GFR = glomerular filtration rate
MAG3 = mercaptoacetyltriglycine
UTI = urinary tract infection
VCM = video cystometry
VCU = voiding cystourethrography
VUR = vesicoureteral reflux

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INFANTS with high grade vesicoureteral reflux are regarded as a special group with their own characteristics concerning renal damage, gender, resolution rate and probably causative mechanism. They often present early and some cases are detected prenatally. These patients have a high incidence of hypoplastic kidney, which has been suggested to represent maldevelopment in utero rather than a consequence of urinary tract infection.[1–6] However, kidney damage due to urinary tract infection is also seen in children with high grade reflux, and often is referred to as focal damage.[4–6]

In the past surgical intervention was considered necessary in infants with high grade VUR and recurrent UTI to prevent further renal damage. Recently there has been a trend toward more conservative management and delayed surgical intervention. A

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Table 1. *VUR grade at study inclusion*

Grade	No. Gender		Total No.
	M	F	
Unilat:			
III	3	2	5
IV	13	7	20
V	8	1	9
Bilat:			
III/I–III	6	7	13
IV/I–IV	19	13	32
V/I–V	31	5	36
Totals	80	35	115

major reason for this trend is that the spontaneous resolution rate is reportedly high in infants with a prenatal diagnosis.[2] We found a similar high spontaneous resolution rate in our 115 cases of high grade VUR, of which the majority were diagnosed after UTI. This patient series has been described previously.[7] These records have now been further analyzed, focusing on renal damage and function. The main aim of this study was to assess renal status through time but risk factors for deterioration were also evaluated.

MATERIALS AND METHODS

The study received approval from the local ethics committee and parents of the patients gave consent to the investigation program. Patients younger than 1 year who were born between 1992 and 1997 with high grade VUR and treated at Queen Silvia Children's Hospital were consecutively included in this prospective observational study. There were 80 boys (70% of patients) and 35 girls (30%). The diagnosis was made after prenatal ultrasound (routinely performed at 16 to 18 weeks of gestation in all pregnant women in the region) in 30 infants (26%) and after acute pyelonephritis in 82 (71%). Two boys presented with failure to thrive and 1 presented with an abdominal mass.

Median patient age at diagnosis of VUR, counting the first VCU, was 2.7 months (1.6 months in boys and 5 months in girls, range 0.03 to 11.7). A total of 81 patients (70%) had bilateral VUR. Distribution of VUR grade at study inclusion is outlined in table 1. Distribution of VUR in the group diagnosed prenatally was grade V in 16 patients (53%), grade IV in 12 (40%) and grade III in 2 (7%). The proportion of grade IV to grade V reflux was higher in this group than in cases diagnosed after pyelonephritis ($p = 0.022$).

Patients were investigated according to a program that included repeat VCM, scintigraphy and renal function testing (table 2). Surgical intervention of VUR was intentionally late and median age at surgery in 35 patients was 42 months (range 14 to 91). Indications for surgery were persistent high grade VUR at the end of the observational time and/or repeat breakthrough infections.

VCM, which included simultaneous VCU and cystometry, was done with computerized equipment according to a method described previously.[7] All VCUs were reviewed by a pediatric radiologist and pediatric urologist to determine the grade of reflux according to the International System.[8] VUR resolved spontaneously in 31 cases (27%) and was downgraded to grade II or less in 14 (12%). No further VCM was done in cases of spontaneous resolution of VUR or after surgical intervention. Results of VUR resolution have been published previously,[7] and are not further analyzed in this report.

Renal parenchymal abnormality was evaluated based on renal scintigraphy consisting of static ^{99m}technetium DMSA (17 patients, 15%), dynamic ^{99m}technetium MAG3 (37, 32%) or both (61, 53%). The investigations were performed according to European standards.[9,10] MAG3 scintigraphy was the method of choice in the presence of severely dilated renal pelvis and calices, in which obstruction or delayed outflow was suspected. Otherwise DMSA was used. All renal scintigrams were reviewed by a team of specialists (RS, UJ, SS). Renal abnormality was classified as either focal or generalized. A small kidney with reduced tracer uptake or diffuse parenchymal anomaly was classified as generalized abnormality, of which none had split function greater than 45% (if unilateral damage). Focal abnormality or damage was defined as areas with reduced uptake or indentation of the renal outline.

In some of the scintigrams performed at a few months of age interpretation and characterization of the abnormality were difficult due to poor quality of the investigation. In the complete series of investigations the type of abnormality became more obvious and, therefore, the final scintigraphic investigation was used for characterization of renal status. All investigations were included to determine changes in renal status through time. Renal damage and function were also monitored after surgical intervention. Repeat investigations were available in 108 patients.

Table 2. *Studies performed in patients with high grade VUR since infancy*

	VCM + Free Voiding	Scintigraphy	Plasma 51Cr EDTA
Median No. evaluations/pt (range)	3 (2–5)	4 (1–10)	3 (1–11)
Median mos age at first evaluation (range)	2.7 (0.03–12)	4.7 (0.2–54)	7.7 (0.5–72)
Median mos followup (range)	36 (2–69)	62 (4–135)	53 (1–145)
Median mos followup after last evaluation:			
With VUR resolution	27	52	51
Without VUR resolution	39	68	55
p Value	0.006	0.008	0.5

After resolution of reflux no additional VCMs were performed.