

# IMPACT OF VESICoureTERAL REFLUX ON THE SIZE OF RENAL LESIONS AFTER AN EPISODE OF ACUTE PYELONEPHRITIS

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## ABSTRACT

**Purpose:** We determined the impact of vesicoureteral reflux (VUR) on the size of renal lesions in children after an episode of acute pyelonephritis.

**Materials and Methods:** A total of 161 children (mean age 2.44 years) with acute pyelonephritis were studied. All had renal lesions on dimercapto-succinic acid scintigraphy done at admission to the hospital. A second dimercapto-succinic acid scan was performed at 3 months. Voiding cystourethrography was done at 6 weeks and VUR was graded I to V. For each renal unit layouts of renal lesions were drawn, and the damage surface was calculated and reported for the total surface of the kidney.

**Results:** Mean size of acute lesions and scars increased with severity of reflux ( $p < 0.0001$ ), with an important overlap of individual values. Mean size of renal scars in the group of renal units with acute lesions was  $5.8\% \pm 8.5\%$  in patients without VUR,  $9.9\% \pm 7.3\%$  in those with grade I reflux,  $7.7\% \pm 11.0\%$  in those with grade II reflux,  $17.7\% \pm 14.7\%$  in those with grade III reflux and  $17.4\% \pm 27.7\%$  in those with grade IV reflux ( $p < 0.001$ ). The size of renal lesions decreased significantly with time. The rate of regression of lesions decreased with increasing reflux. When analyzed according to 3 age groups sizes of scars increased significantly with age.

**Conclusions:** VUR has an impact on the size of renal lesions after an episode of pyelonephritis. Children with a grade III or IV reflux are more likely to have larger renal scars. On the other hand, acute lesions of important size may develop even in the absence of VUR.

**KEY WORDS:** pyelonephritis, cicatrix, vesico-ureteral reflux, technetium Tc 99m dimercaptosuccinic acid

Acute pyelonephritis in children often leads to irreversible lesions of renal parenchyma that are still present several months after the acute episode and defined as renal scars.<sup>1</sup> It has been shown that the inflammatory process, which appears early in the course of the disease, is responsible for scar formation.<sup>2</sup> Children with renal lesions after repeated episodes of acute pyelonephritis are at risk for development of hypertension and impairment of renal function.<sup>3–5</sup>

In pediatric pyelonephritis acute lesions of the kidney on dimercapto-succinic acid (DMSA) scan are observed in 42% to 92% of patients, leading to permanent renal damage in 36% to 68%.<sup>6–10</sup> The gold standard for the diagnosis of these lesions is DMSA scintigraphy, which has good sensitivity and specificity.<sup>6, 11</sup>

Vesicoureteral reflux (VUR) is classically considered a risk factor for the development of renal scarring but the development of scars has been observed to occur in the absence of VUR.<sup>6–9</sup> This finding raises the question of the exact correlation between VUR and renal lesions, and of the importance of VUR in the etiology of renal scarring. In the literature there is a lack of information concerning the size of renal lesions on DMSA scan. Several studies demonstrate DMSA results as positive or negative. A positive DMSA scan may correspond to small lesions of limited clinical significance. Thus, it is important to measure the size of renal lesions on DMSA scan, especially if one wants to correlate renal damage with potential risk factors such as VUR.

The aim of this study was to determine the impact of VUR on the size of acute renal lesions and resultant renal scars. For this purpose the frequency of renal lesions and their

precise size on DMSA scintigraphy were analyzed during acute episodes and at 3 months.

## METHODS

Patients with clinically suspected pyelonephritis had a urine sample taken for culture and a blood sample for blood count, C-reactive protein determination and culture. Clinical suspicion was defined as fever greater than 38.5°C, general signs of feeding difficulties, vomiting, irritability and abdominal or flank pain in older children. If the urine culture was positive, renal ultrasound and DMSA renal scan were performed in the acute phase (3 to 5 days). All patients presented initially between 1994 and 1997.

Patients were included in the study if they had a positive urine culture and an acute lesion on the first DMSA renal scintigraphy. A positive urine culture was defined as 100,000 colonies per ml or greater with 1 type of bacteria (2 if the bacteria were *Escherichia coli* and *Enterococcus faecalis*) in a urine sample collected in a sterile bag, or any colonies if the sample was collected by suprapubic puncture of the bladder. Patients were excluded if they had obstructive renal disease, incomplete radiological files or a scintigram of less than 1 × 0.8 inches, which does not allow precise measurement of the surface of the lesions.

Renal scintigraphy was performed according to standard techniques—3 to 4 hours after an intravenous injection of DMSA labeled 3.7 MBq <sup>99m</sup>technetium per kilogram (with a minimum dose of 18.5 MBq and a maximum dose of 185 MBq) image acquisition was performed with a GCA-9300A/HG gamma camera connected to a computer (Toshiba Medical Systems Co., Japan). Six different views were obtained (1 posterior, 2 posterior oblique, 1 anterior and 2 anterior oblique projections). Acute lesions were defined as a

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decreased uptake of isotope in at least 2 different views. Scars were defined as persistent changes in the same location as in the first DMSA scan. Every image was independently assessed by 2 experienced radiologists who used standard criteria previously defined by Patel et al.<sup>12</sup> To calculate the precise size of renal lesions, each image was assessed regardless of clinical history and presence or absence of vesicoureteral reflux. Each outline of lesion and kidney was drawn on the view of the scintigram where the lesion was the largest. If multiple lesions were present, surface areas were added together. The corresponding surfaces were calculated and compared to the total surface of the kidney. Sizes of lesions were expressed as percentage of total kidney surface.

To diagnose VUR, voiding cystourethrography (VCUG) was done 6 weeks after the diagnosis. Reflux was classified according to the gradation of the International Reflux Study committee, grade I to V.<sup>13</sup> The surfaces of renal lesions were correlated with the result of the VCUG. Size of renal lesions was analyzed on first and second DMSA scan.

To study the relation between clinical characteristics, grade of reflux and renal lesions, in case of bilateral reflux and/or lesion the side where the reflux and/or lesion was greatest was considered. Acute renal lesions and scars were further analyzed according to 4 groups of patients—those with left dominant reflux (defined as left unilateral reflux or bilateral reflux with a more important grade on the left side), those with right dominant reflux (defined as right unilateral reflux or bilateral reflux with a more important grade on the right side), those with bilateral reflux of the same grade and those without reflux. Finally, renal units with acute lesions were analyzed according to 3 age groups—less than 1 year, 1 to 5 years and more than 5 years.

Results were given in terms of renal units as mean  $\pm$  standard error. Differences between percentages were analyzed using the chi-square test. Renal lesion sizes were compared using the Kruskal-Wallis nonparametric test and Dunn's posttest. Differences between means were analyzed using the Mann-Whitney U test and Wilcoxon rank sum test for paired data. The effect of reflux on the progression of lesions and the effect of clinical characteristics on the size of scars were analyzed using analysis of variance. Statistical analysis was performed using the Stata statistical software package (StataCorp LP, College Station, Texas) and Prism software (GraphPad Software, Inc., San Diego, California).

## RESULTS

**Characteristics of study population.** A total of 161 children (age range birth to 11.2 years, 120 girls and 41 boys) were included in this study. Of the boys 78% were younger than 1 year at the time of diagnosis. Mean age was 1.17 years (median 0.47) for boys and 2.87 years (1.82) for girls. Clinical data are outlined in table 1.

The impact of the clinical parameters on the size of renal scars was studied using analysis of variance. The presence of a previous urinary tract infection (UTI, 12 patients) and abnormal voiding habits (9) were found to be significantly related to the size of renal scars ( $p < 0.001$  and  $p = 0.04$ , respectively). Mean size of renal scars in the group of patients with previous UTI was  $19.1\% \pm 20.6\%$  compared to  $8.1\% \pm 10.5\%$  in the other patients ( $p = 0.038$ ).

TABLE 1. Characteristics of study population

	No. Pts
Abnormal voiding habits	9
Abnormal bowel habits	7
Previous UTI	12
Abnormal urethra on VCUG	6
Abnormal bladder on VCUG*	5

\* One patient had bladder thickening and 4 had bladder diverticuli.

**Frequency of renal lesions and VUR.** According to the inclusion criteria, each child had a renal lesion on the first DMSA scan. In terms of renal units, 197 of 322 renal units (61%) had lesions on the first DMSA scan. On the second DMSA scan performed at 3 months 80% of renal lesions exhibited partial or total regression, and a renal scar was present in 104 of 322 renal units (32%). Of 322 renal units vesicoureteral reflux was diagnosed in 89 (28%) on VCUG at 6 weeks. Grades of reflux were distributed as follows—15 renal units (17%) grade I, 38 (43%) grade II, 26 (29%) grade III and 10 (11%) grade IV.

Among renal units with acute lesions 47% in the group without reflux had renal scars, 60% had scars in the group with reflux grades I and II, and 78% had scars in the group with reflux grades III and IV. The frequency of renal scars increased with the severity of reflux ( $p = 0.003$ ).

**Size of renal lesions and VUR.** When analyzed according to the grade of reflux an overlap of individual values was observed. Nevertheless, the mean size of acute renal lesions increased when reflux was present (Mann-Whitney U test between renal units with and without reflux,  $p < 0.0001$ , fig. 1, A). Of the subgroup of renal units with acute lesions the mean size of renal lesions was  $19.1\% \pm 12.1\%$  in the group without VUR,  $25.2\% \pm 8.8\%$  in the group with grade I VUR,  $18.0\% \pm 10.4\%$  in the group with grade II VUR,  $24.0\% \pm 12.4\%$  in the group with grade III VUR and  $27.6\% \pm 25.4\%$  in the group with grade IV VUR.

Overlap was also observed for renal scars. Mean size increased with severity of reflux (Kruskal-Wallis nonparametric test,  $p < 0.0001$ , fig. 1, B). Of the subgroup of renal units with acute lesions the mean size of renal scars was  $5.8\% \pm 8.5\%$  in the group without VUR,  $9.9\% \pm 7.3\%$  in the group with grade I VUR,  $7.7\% \pm 11.0\%$  in the group with grade II VUR,  $17.7\% \pm 14.7\%$  in the group with grade III VUR and  $17.4\% \pm 27.7\%$  in the group with grade IV VUR (Kruskal-Wallis nonparametric test,  $p < 0.001$ ). The risk for a child having a renal scar of more than 25% of the surface of the kidney increased with grade of reflux ( $p = 0.015$ , table 2).

When analyzing regression of lesions at 3 months in the group of renal units with an acute lesion the size of renal lesions decreased significantly with time in all groups. The grade of reflux affected significantly the rate of regression of lesions. The greater the reflux, the lesser the regression (ANOVA,  $p < 0.001$ , table 3).

To highlight the correlation between VUR and renal lesions for a given patient, renal lesions were analyzed by subtracting the size of lesions of 1 side from the other (right minus left) for each patient and analyzed according to 4 groups—patients with left dominant reflux, right dominant reflux, reflux of same grade and without reflux. In patients with left dominant reflux the mean size of acute renal lesions and scars on the left side was significantly larger than in those with right dominant reflux ( $p < 0.05$  and  $p < 0.01$ , respectively), indicating that renal lesions were more extensive when reflux was present on the same side.

**Size of renal lesions and age.** The frequency and size of renal scars were analyzed according to 3 age groups—younger than 1 year, 1 to 5 years and older than 5 years. The frequency of renal scarring increased with age ( $p = 0.0003$ ). When considering only renal units with an acute lesion sizes of scars increased significantly with age ( $p < 0.0001$ ), and posttest revealed statistically significant differences between the group of patients younger than 1 year and the other 2 age groups ( $p < 0.001$ , fig. 2).

## DISCUSSION

Renal lesions may lead to hypertension and renal function impairment. Thus, one of the main goals of pyelonephritis management is to decrease the occurrence of renal scars. As reflux has traditionally been considered a risk factor for renal

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