Renal Scarring in Familial Vesicoureteral Reflux: Is Prevention Possible?

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Purpose: Detailed knowledge about risk factors for renal scarring in familial reflux is necessary to decide whether these factors could be influenced by early screening and treatment of siblings. We evaluated the prevalence of and risk factors influencing renal scarring in familial vesicoureteral reflux.

Materials and Methods: We reviewed the medical records and dimercapto-succinic acid scans of 306 children with familial vesicoureteral reflux. Scarring was classified as mild, moderate and severe. The impact of urinary tract infections, patient sex, reflux grade and age at diagnosis on renal scarring was evaluated.

Results: The prevalence of renal scarring was identical at 36% in 142 index patients and 74 siblings presenting with urinary tract infection but it was only 10% in 87 asymptomatic siblings ($p < 0.001$) The difference between siblings with and without urinary tract infection was only statistically significant for mild scarring (23% vs 4.6%, $p < 0.001$). It did not attain significance in those with moderate to severe scarring (13.5% vs 5.7%). Moderate to severe scarring was significantly more common in grade V than in grade IV refluxing units (43% vs 10%, $p < 0.0001$) and in male than in female siblings (15.8% vs 3.4%, $p = 0.012$). Mild scarring was not significantly associated with reflux grade or patient sex. Children diagnosed before age 3 years showed significantly less scarring than patients diagnosed later (23% vs 41%, $p < 0.002$).

Conclusions: The development of mild renal scarring seems to mainly depend on urinary tract infections, while moderate and severe scarring are also associated with high grade reflux and male sex. Early detection and treatment may prevent further urinary tract infections as well as reflux related kidney damage.

Key Words: vesico-ureteral reflux, genetics, kidney, cicatrix, mass screening

Vesicoureteral reflux is the most common urological abnormality in children, affecting 1% to 2% of the pediatric population and 30% to 40% of children presenting with UTI.[1,2] Reflux associated nephropathy is a major cause of childhood hypertension and chronic renal failure.[3,4] The hereditary and familial nature of VUR is now well recognized.[5,6] Familial clustering of VUR has been described by several groups at a prevalence of 27% to 51% in siblings of children with VUR.[7–9] Therefore, siblings of patients with VUR represent a population at high risk for VUR.

However, whether screening asymptomatic siblings of children with VUR is beneficial is still controversial.[10] Several groups have suggested that early detection and treatment in asymptomatic siblings with VUR may be beneficial for preventing renal damage.[7,11,12] On the other hand, the lack of a sensitive, noninvasive screening method has limited the acceptance of screening asymptomatic siblings as daily routine. Invasive screening tests in asymptomatic siblings can only be justified if early detection and treatment of reflux could beneficially influence the development or progression of reflux associated kidney damage. Detailed knowledge about the risk factors of renal scarring in familial reflux is necessary to determine whether these factors could be influenced by early screening and treatment of siblings. We evaluated the prevalence of and identified risk factors influencing renal scarring in familial VUR.

PATIENTS AND METHODS

Between 1998 and 2003 we collected data on 159 white families with at least 2 siblings (range 2 to 5) who had VUR. A total of 345 children of these families were identified as having VUR on VCUG. Siblings of index patients were identified with VUR after a symptomatic UTI, as were index patients usually, or they were asymptomatic and identified by a sibling screening program.

DMSA renal scans to assess renal scarring were available in 306 of these children (89%), who formed the study group. Their medical records and DMSA scans were reviewed retrospectively. Of the 39 patients who did not have a DMSA scan available 14 (36%) were index patients, 7 (18%) were siblings with UTI and 18 (46%) were asymptomatic siblings.

Data collected were age at diagnosis, patient sex, symptomatic UTI before diagnosis, reflux grade I to V according to the International Reflux Study Committee, and the presence and grade of renal scarring. Age at diagnosis was defined as patient age at the first VCUG. Renal scarring was evaluated by ^{99m}technetium-DMSA radionuclide scan and classified into 3 groups, including mild—focal defects with relative uptake above 40%, moderate—relative uptake of renal radionuclide between 20% and 40%, and severe—shrunken

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kidney with relative uptake less than 20%.[12] In cases of bilateral scarring the scarring grade was not classified by split renal function, but rather based on image interpretation by a radiologist. In children presenting with UTI DMSA scans were performed at least 4 to 6 months after UTI. DMSA scans in asymptomatic siblings were performed between 1 and 4 months after the first VCUG.

The influence of UTI, patient sex and age at diagnosis on renal scarring was analyzed in each patient. In cases of bilateral renal scarring the more severe grade of renal scarring was assigned. The impact of reflux grade on renal scarring was analyzed separately in every refluxing renal unit. The Fisher exact and Mann-Whitney U tests were used for statistical analysis with $p < 0.05$ considered statistically significant.

RESULTS

Patients

Of the 129 boys and 177 girls with familial VUR 52 boys and 90 girls were index patients, 34 boys and 40 girls were siblings diagnosed after symptomatic UTI, 41 boys and 46 girls were asymptomatic siblings and in the remaining 3 siblings, including 2 boys and 1 girl, it was not clear from the charts whether they had had UTI before diagnosis. These 3 children showed no renal scarring on DMSA scan. Median age at VUR diagnosis was 1.57 years (range newborn with reflux detected on prenatal ultrasound to 12 years). Median age at diagnosis in index patients was significantly higher than in screened siblings (2.1 vs 0.6 years, $p < 0.0001$). However, it was not significantly different from that in siblings detected after a UTI (median 2.4 years).

The first DMSA scan showed renal scarring in 87 of the 306 patients (28%). Renal scarring was classified as mild in 41 cases (47%), moderate in 34 (39%) and severe in 12 (14%).

UTI and Renal Scarring

Renal scarring was found in 51 of 142 index patients (36%). Siblings presenting with UTI had exactly the same prevalence of renal scarring as index patients (27 of 74 or 36%) but only 9 of the 87 screened asymptomatic siblings (10%) showed renal scarring ($p < 0.001$). Mild scarring was significantly more common in siblings presenting with than in siblings without UTI (17 of 74 or 23% vs 4 of 87 or 4.6%, $p < 0.001$). However, although the prevalence of moderate to severe scarring was higher, it was not statistically different between siblings presenting with UTI and siblings without a history of UTI (10 of 74 or 13.5% vs 5 of 87 or 5.7%, $p = 0.1$). Index patients who also had UTI had a significantly higher rate of moderate to severe scarring than screened asymptomatic siblings (31 of 142 or 22%, $p = 0.001$). Figure 1 shows the different grades of renal scarring in index patients and siblings.

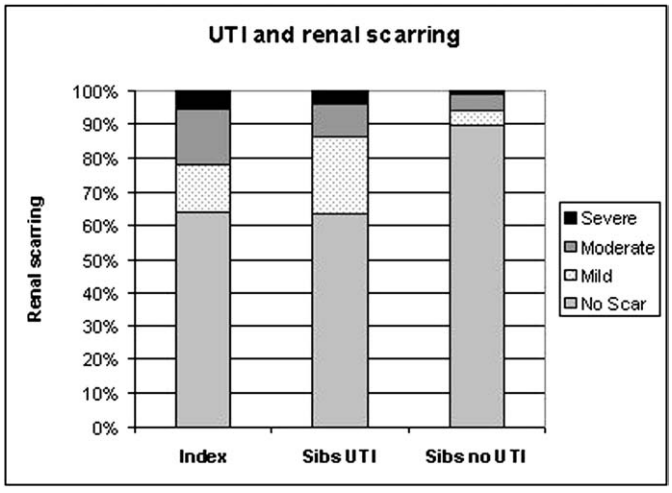

FIG. 1. Different renal scarring grades in index patients, siblings with UTI and screened siblings. Siblings without UTI had significantly less mild scarring than siblings presenting with UTI ($p < 0.001$). Difference in moderate to severe scarring was not statistically significant between 2 groups.

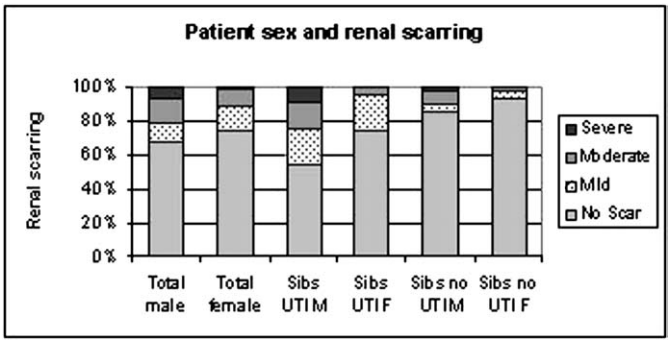

FIG. 2. Moderate to severe renal scarring was significantly more often found in male (*M*) than in female (*F*) patients ($p = 0.015$). There was no significant difference in prevalence of mild renal scarring between sexes. Higher incidence of moderate to severe scarring in males vs females was most pronounced in siblings with history of UTI ($p = 0.037$).

Patient Sex and Renal Scarring

Figure 2 shows the different grades of renal scarring in male and female patient groups. Renal scarring was found slightly more often in male than in female patients (42 of 129 or 33% vs 45 of 177 or 25%, p not significant). Moderate to severe scarring was significantly more often found in male than in female siblings (12 of 77 or 15.8% vs 3 of 87 or 3.4%, $p = 0.012$). In contrast, the prevalence of mild renal scarring was not significantly different between male and female siblings (9 of 77 or 11.7% and 10 of 87 or 11.5%, respectively). Interestingly male siblings presenting with UTI had a significantly higher prevalence of moderate to severe renal scarring than female siblings presenting with UTI (8 of 34 or 23.5% vs 2 of 40 or 5.0%, $p = 0.037$). There was no difference in the incidence of mild renal scarring between these male and female groups (20.1% and 20.0%, respectively).

Reflux Grade and Renal Scarring

The number of refluxing units instead of patients was used for this part of the study. Table 1 shows the results of renal scarring stratified by reflux grade. As expected, renal scarring was significantly more common in grade V refluxing units than in grades I to IV refluxing units (each $p < 0.001$, fig. 3). There was no significant difference between grades I to IV refluxing units. Grade V refluxing units had a significantly higher prevalence of moderate to severe renal scarring than grade IV units (43% vs 10%, $p < 0.0001$), while there was no significant difference in moderate to severe scarring between grades I to IV refluxing units. No significant difference in mild renal scarring was found between any reflux grades. Of the 35 refluxing units