SCINTIGRAPHIC SCREENING IN THE DETECTION OF RENAL SCARRING IN SIBLINGS OF CHILDREN WITH PRIMARY REFLUX

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Abstract- The correlation of vesicoureteral reflux (VUR), urinary tract infection (UTI) and renal scarring is well known. Several risk factors for renal parenchymal lesions have been reported previously. We determine the incidence of renal parenchymal damage and outcome in the siblings of children with primary VUR. A total of 96 siblings of patients with VUR, were evaluated with direct voiding cystography, 99^{m}-technetium (Tc)-dimercaptosuccinic acid (DMSA) renal scintigraphy and renal ultrasonography (US). Of 96 siblings, 34 were found to have VUR, representing an incidence of 35.4%. The majority of siblings with abnormal DMSA scans were asymptomatic. Parenchymal abnormalities were determined by DMSA in 23 (69.6%) of the 33 siblings studied (37 of 46 refluxing renal units or 80.4% P <0.001). Of these, 10 (30.3%) were normal. Renal damage was mild, moderate and severe in 30.3%, 54.5%, and 15.2% of children, respectively. Renal US in 34 siblings with VUR was normal in 27 (79.4%) and abnormal in 7 (20.5%). Of the 33 siblings with VUR who had both renal cortical scintigraphy and renal US, DMSA and US findings were abnormal in 23 and 7 of the siblings, respectively. Parenchymal abnormalities on scintigraphy were associated with mild-to-moderate reflux in 51.5% and severe reflux in 72.7% renal units. This study confirms a significant overall incidence of renal parenchymal damage in 69.6% and VUR in 35.4% of siblings studied. Most importantly, the lack of symptoms within the siblings group can not be used as a reason to avoid screening process. DMSA scintigraphy of asymptomatic siblings appears to be beneficial in preventing renal injury.

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Key words: DMSA scintigraphy, Vesicoureteral reflux, Sibling reflux, Renal scarring, Children

INTRODUCTION

Vesicoureteral reflux (VUR) is the most common congenital anomaly of the urinary tract in children (1). It is widely reported that vesicoureteral reflux combined with urinary tract infection has an important role in renal scarring process (2), and is also frequently identified in asymptomatic siblings of children with VUR (3).

The incidence of VUR is 30–51 times higher in first-degree relatives of patients with VUR than in the general population (4-7). Furthermore, the transmission of VUR from parent to child has been reported as many as 66% (8), and 43% of neonates born to mothers with reflux nephropathy were found to have VUR (9). Reflux in symptomatic and asymptomatic siblings is a risk factor for pyelonephritis, which can result in permanent renal damage, hypertension or chronic renal failure (10-13). Reflux nephropathy is responsible for 5% to

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15% of renal failure in Adults and it is also the most cause of severe hypertension in children (14 -16). Associated renal scarring has been reported in 4.7%-41% of siblings with VUR (3, 10, 11, 15, 17, 18). However, there are relatively few data on the screening for renal damage with DMSA scintigraphy in siblings of children with VUR with varying results (10, 11, 17, 19, 20).

Renal cortical scintigraphy with 99^{m} technetium (Tc) dimercaptosuccinic acid (DMSA), although not prefect, appears to be the best clinically applicable standard of reference for the diagnosis of acute pyelonephritis (APN). It is considered the most sensitive technique for the identification of the renal parenchymal change in APN, as well as in the detection of scarring (21-23).

In the present prospective study, we defined the association of renal injury by determining the incidence and characteristics of renal abnormalities on DMSA renal scintigraphy, also this review was done to identify the overall incidence and severity of reflux in siblings of children with VUR.

MATERIALS AND METHODS

From April 1994 to September 2004, we prospectively screened 96 siblings of 80 eligible index patients with an awake voiding cystourethrography (VCUG) or direct radionuclide cystography (RNC) as soon as the VUR of the index case was diagnosed, irrespective of the presence of symptoms and/or history of documented urinary tract infection (UTI). A group of 96 siblings (62 families with 1 sibling, 15 families with 2 siblings, 2 families with 3 siblings, and 1 family with 4 siblings) were evaluated. Of the families with 2, 3 and 4 siblings 29, 4 and 1 sibling were available for study respectively. All children within this group had primary reflux. The mean age at presentation of the 59 girls and 37 boys was 65 months (range 3 months to 13 years). In order to estimate the relationship between the incidence renal parenchymal damage, reflux and sibling age, the patient population was divided into two subgroups: siblings aged 0–6 years and those over 6 years. The first group consisted of 26 of 34 (76.4. %) subjects and the second of the remaining 8 (23.6%) subjects. Siblings with structural abnormalities such as neurogenic bladder, posterior urethral valves, ureterocele, or other congenital anomalies were excluded from the study. In the early phase of the study DMSA renal cortical scintigraphy was performed in siblings with VUR. The intravenously injected contrast activity was adjusted to the patient's weight, according to a standard schedule (24); 3 h after injection of the tracer, one posterior, one anterior, and two posterior oblique images of the kidneys were acquired, with the patient prone below the camera. The fractional left and right renal activity was calculated for each kidney. Kidney uptake of 45%–55% of the total renal activity was considered normal (symmetrical renal split function).

The renal scintigraphic patterns were independently interpreted by two senior nuclear medicine physicians and the criteria used for the interpretation of the images did not change during the period of the investigation. A kidney of regular shape and a tracer uptake that appeared to be homogenous was considered normal.

Single or multiple cortical defects and focal or diffuse patterns in one kidney were considered abnormal (25-27). The cystograms were obtained with either iodinated contrast medium or a direct radionuclide technique. The radionuclide cystograms were interpreted as showing the presence or absence of reflux. VUR was graded as mild, moderate, or severe by radionuclide technique (1). Demonstration of tracer reflux in only the ureter by RNC or grade I VUR on VCUG using the International Reflux Study Grading System was considered mild. Tracer reflux in a nondilated renal pelvis on RNC or grade II and III VUR on VCUG was graded moderate.

Reflux of tracer into a grossly dilated renal pelvis on RNC or grade IV and V reflux on VCUG was considered severe (1, 28). Cases of bilateral reflux in which the grade differed on each side were assigned the grade of the more severely affected side. When VUR was diagnosed, antibiotic prophylaxis was started with a single daily dose given at night. This included those without prior symptoms or known UTI.

All siblings underwent ultrasonography (US) by a pediatric radiologist. The kidneys were studied by sonography for size, shape, parenchymal

echogenicity, corticomedullary differentiation, irregularity of the kidney outlining, and parenchymal reduction. Reflux was considered to have resolved when follow-up radionuclide cystograms demonstrated no reflux. In addition to recording the resolution of reflux, any change relative to reflux grade at diagnosis was noted. Siblings with VUR were evaluated using radionuclide voiding cystography and renal cortical scintigraphy initially and every 12 months thereafter. Treatment consisted of prophylactic antibiotics in all children with reflux. Urine cultures were obtained every 3 months at follow-up visits.

Two negative voiding cystourethrograms 1 year apart were required to discontinue prophylaxis. The chi-squared procedure was used to determine the statistical significance of the relationships between variables. A P value below 0.05 was considered statistically significant.

Before beginning the investigation, the nature, aim, potential risks, and benefit of cystourethrography and cortical scintigraphy were explained to the parents or guardians and oral informed consent was obtained. The study was approved by the ethics committee of Tehran University of Medical Science.

RESULTS

There were 96 siblings of the 80 index patients in the study; 14 index patients were male and the remaining 66 were female. The age of the index patients ranged from1 month to 15 years (mean, 4 years and 3 months). Reflux was bilateral in 42 and unilateral in 38 index patients. Of the 80 index patients with a first documented pyelonephritis, 62 (77.5%) had abnormal cortical scintigraphy and 18 (22.5%) had normal kidneys. Thirty of 38 patients with unilateral reflux had mild or moderate reflux. Of the 42 patients with bilateral reflux, 15 had severe reflux.

The siblings group consisted of 37 boys and 59 girls. Of the 96 siblings, 34 (8 boys and 26 girls) were found to have VUR, representing an incidence of 35.4%. The mean age at study entry of the 37 boys and 59 girls was 65 months (range 3 months to 13 years).

Among the 34 refluxing siblings, 10 had a history of symptomatic UTI. The VUR was unilateral in 21 and bilateral in 13 (Table 1), thus 47 of 68 units had VUR. Reflux was mild in 16 siblings, moderate in 11, and severe in 7. Of the 47 refluxing units, 23 were mild (grades I and II), 13 moderate, (grade III) and 11 were severe (grades IV and V). The relationship between the severity of VUR and laterality is shown in Table 2.

Of the 21 siblings with unilateral reflux, 13 had mild, 7 moderate, and 1 had severe reflux. In the group with bilateral reflux, 3 had mild, 4 had moderate and 6 had severe reflux. Of the 34 siblings with VUR, 82.3% had normal kidneys on sonograms and parenchymal scarring was evident in 17.7%. Thirty three out of 34 siblings with VUR had DMSA scintigraphy. Of these, 10 (30.3%) were normal and 23 (69.6%) showed parenchymal abnormalities (30.3% mild, 54.5% moderate, and 15.2% severe). One sibling refused renal scintigraphy. Parenchymal abnormalities were determined by 99^{m} Tc-DMSA renal scintigraphy in 23 of the 33 siblings studied (37 of 46 refluxing renal units or 80.4%, $P < 0.001$). DMSA was normal in 10 cases. Of the group with normal DMSA, 4 siblings with a symptomatic UTI had evidence of cystitis. Of the 23 siblings with abnormal DMSA scans, 17 had asymmetrical split function with no shape defect and 6 had a parenchymal defect. Of this group, 4 (17.3%) were over 6 years of age and 19 (82.6%) were under 6 years.

All of 4 siblings over 6 years with abnormal DMSA scans were asymptomatic. Among the 19 siblings below 6 years with abnormal DMSA scans, only 6 had a history of symptomatic UTI, 1 with evidence of pyelonephritis (*i.e.*, high fever with leukocytosis) and the remaining 5 had cystitis. Overall, 74% of siblings with abnormal DMSA scans were asymptomatic. Parenchymal abnormalities on scintigraphy were associated with

Table 1. Reflux status in 96 siblings according to laterality

	Siblings	
Laterality of reflux	No.	%
None	62	64.6
Unilateral	21	21.9
Bilateral	13	13.5
Total	96	100

Table 2. The relationship between the severity of VUR and laterality in 34 siblings with reflux

Grade of VUR	Unilateral (No.)	Bilateral (No.)	Total (No. %)	
Mild (I, II)	13	3	16	47
Moderate (III, IV)	7	4	11	32.4
Severe (V)	1	6	7	20.6
Total	21	13	34	100

Abbreviation: VUR, vesicoureteral reflux.

mild-to- moderate reflux in 51.5% and severe reflux in 72.7% renal units (Fig. 1).

Renal US in 34 siblings with VUR was normal in 27 (79.4%) and abnormal in 7 (20.5%). Of the 33 siblings with VUR who had both renal cortical scintigraphy and renal US, DMSA and US findings were abnormal in 23(69.6%) and 7 (21.2%) of the siblings, respectively. US was normal in all siblings with normal 99^{m}Tc-DMSA scintigraphy findings.

Topographic analysis of the 66 focal damages showed that 48.4 % were localized to the upper poles, 15.1% to the middle third, and 36.3% to the lower poles of the kidneys. Outcomes were assessed in the 34 cases of VUR. At a mean follow-up of 30 months (range 2–84 months), 7 siblings underwent ureteral reimplantation. The indications for surgery were persistent high-grade reflux (3 girls and 1 boy) and breakthrough infection (3 girls) while the patients were on antibiotic prophylaxis. In the 1 sibling with breakthrough UTI, reflux was mild to moderate. Five siblings underwent endoscopic correction. Reflux resolved completely in 5 patients, and was downgraded in 4 on medical treatment and 13 are still being observed on antibacterial prophylaxis with a reasonable expectation of spontaneous cessation of the reflux.

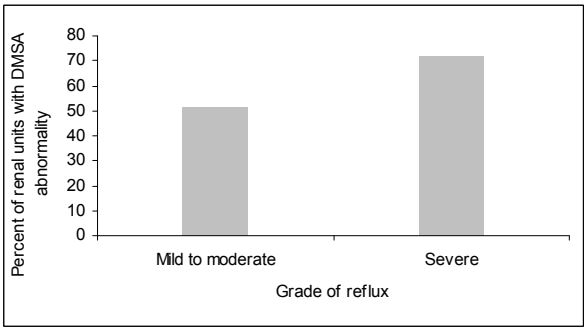

Fig. 1. Correlation of 99^{m} technetium-dimercaptosuccinic acid (99^{m}Tc-DMSA) renal scintigraphy abnormalities with reflux grade.

DISCUSSION

There have been conflicting results in the literature on the incidence of renal damage in siblings of children with known reflux (10, 11, 17, 29). In this study, the percentages of siblings with renal parenchymal damage were higher to that described in the literature, where incidences vary between 3% and 41%% (3, 10, 11, 15, 17, 29-31). In addition, the high incidence of reflux in the siblings of patients with primary reflux is confirmed in the present series, with an overall rate of 35.4% , in accord with previously reported in the literature, where incidences vary between 3% and 51% in siblings of index patients with VUR than in the general population (6, 10, 15, 17, 19, 30).

The debate on VUR is now focusing more on early diagnosis rather than on management (32). Differences in incidence among races, national groups, and multiple members within a given family lend further support to a heritable nature of VUR (33, 34). The recent discovery that primary VUR maps to a locus on chromosome 1 has led to the prospect of genetic screening in the near future (35).

Screening for reflux has been recommended in recognized risk groups (12). We would consider patients at risk to be suitable candidates for such a screening program, including infants and children after the first-time UTI, siblings and offspring of affected individuals, schoolgirls with covert bacteriuria, siblings of multiple gestation births, children with hypospadiasis, and infants with a solitary kidney, ureteropelvic junction obstruction, multicystic dysplastic kidney or prenatally diagnosed hydronephrosis.

The onset of renal scarring is usually early in life, mainly before 5 years old and most frequently before 3 years, but can also occur in older children (9, 19). VUR with renal scarring results in retarded renal growth and hypertension (36), but on the contrary, reflux with no renal scarring does not impair renal growth. However, in VUR associated with renal scarring, contralateral unscarred kidneys often undergo compensatory hypertrophy (37).

Preventing renal scarring appears to be the only available method for preventing hypertension that results from scarred kidneys. Reflux nephropathy is

a major cause of severe hypertension in children and adolescents (16, 38). The severity of hypertension is affected by the extent of renal scarring, the age of the patient, whether both kidneys are involved and the degree of renal insufficiency (37). It may develop several years after the renal damage occurred.

However, in end-stage renal disease, reflux nephropathy is present in 30–40% of children under 16 years old and up to 50% of Caucasian adults below 50 years of age (16, 37, 38). The incidence of scarring in infants with asymptomatic bacteriuria (5–17%) is also significant (10). Thus, renal scarring is critical in the development of hypertension and end-stage renal disease.

Renal damage, the rate of nephrectomy, dialysis and evidence of renal failure are significantly less in siblings who are screened (9, 39). In addition, when reflux discovered in symptomatic siblings, it is usually of high grade and associated with a higher incidence of reflux nephropathy (11). However, if renal injury occurs, it becomes persistent despite spontaneous resolution or surgical correction of the reflux. Moreover, it has been postulated that treating high grade VUR discovered by screening before the initial UTI, might prevent the development of renal scarring (40). Therefore, the prospective identification of reflux before the establishment of renal scarring and adequate treatment of screened siblings may prevent future renal damage and associated morbidity (6).

The likelihood of developing renal scars depends on factors such as the number of symptomatic UTIs, the delay in their treatment and age at diagnosis (31, 38).

Renal cortical scintigraphy with DMSA is considered to be the most sensitive technique for the detection of renal scarring (41, 42). In the index patients the frequency of parenchymal damage was similar to that reported previously (20). In this report DMSA scintigraphy was used to assess renal parenchymal abnormalities in siblings with reflux. Our data revealed a high frequency of renal parenchymal damage (69.6%) in siblings of children with primary reflux. When expressed in number of abnormal renal units, the total number of scarred kidneys was significantly high (37 of 46 refluxing renal units or 80.4%, $P < 0.001$).

VUR appears to occur predominantly in girls. In our population, 26 out of the 34 siblings with reflux were female, which is similar to other published series (41-43).

The results of ultrasound examinations and voiding cystography were compared in order to assess the usefulness of ultrasonography in the screening of siblings of affected children. In the majority of cases (81.1%), we didn't observe any abnormalities in ultrasonographic picture of urinary tract. It confirms the opinions of other investigators that ultrasound examination is not a reliable diagnostic technique for identifying VUR (16, 19, 44, 45). Thus, we recommend that normal renal US should not prevent further evaluation to ascertain VUR. Moreover, replacing renal US by a DMSA renal scintigraphy as previously suggested by Houle *et al.* (16), could be a screening tool in the established protocol of Noe (15). The degree of reflux and the severity of renal parenchymal injury in the siblings with reflux has little correlation to the degree of symptoms or history of UTI. Jerkins and Noe in a prospective study of 104 siblings demonstrated reflux in 32% of the cases. Seventy-three percent of the siblings with reflux were asymptomatic and 15% of those had established renal damage (defined as generalized or localized cortical loss on intravenous urography). It is important to emphasize that 60% of the siblings in the group with renal scarring had no history of UTI (46). In this study 74% of siblings with abnormal DMSA scans were asymptomatic. These findings were in accord with our previous published report and other authors (3, 15, 19, 46). The question remains whether renal damage in asymptomatic siblings is congenital or secondary to undiagnosed urinary-tract infections.

In the present series, reflux was mild in 16 siblings, moderate in 10, and severe in 8 , thus the vast majority (76.4%)of our patients had mild to moderate reflux, with severe in 23.5%. These numbers are consistent with the reports published by numerous authors (10, 17, 46). Of the 21 siblings with unilateral reflux, 13 had mild, 7 moderate, and

1 had severe reflux. These numbers also confirmed previously reported rates (7, 10, 17).

The variability of this incidence may, in part, be influenced by the method of diagnosing renal scarring. Patient age has been shown to be one of the factors primarily affecting the incidence of VUR. Of the 33 siblings with VUR who had renal cortical scintigraphy, 8 cases were over than 6 years old. Fifty percent of this group had abnormal DMSA scan. All of these children were asymptomatic. Prior unrecognized urinary-tract infections might be a possible explanation for renal parenchymal abnormalities in symptom-free siblings. Focal cortical scarring or multiple confluent lesions, due to VUR and UTI is present mostly in the upper or lower pole. The susceptibility of the upper pole to scarring probably results from the anatomy of the papillae in this region and the degree of intrarenal reflux permitted by these papillae. A large percentage of upper pole papillae in children are compound papillae, which have concave surfaces and gaping papillary duct opening onto the calyx with gaping orifices do allow intrarenal reflux and thus expose this region to the harmful effects of VUR (47). In this study topographic analysis of the 66 focal lesions showed that 48.4 % were localized to the upper poles, 15.1% to the middle third, and 36.3% to the lower poles of the kidneys. These data confirm the high percentage of polar damages previously demonstrated by other authors (48-50). Randomized prospective evaluation is required to identify whether early detection by screening methods and the treatment of sterile vesicoureteral would effectively minimize patient morbidity and renal damage.

In conclusion, this study confirms a significant overall incidence of renal parenchymal damage in 69.6% and VUR in 35.4% of siblings studied. Most importantly, the lack of symptoms within the siblings group can not be used as a reason to avoid screening, since the majority of siblings with reflux had no history of urinary tract infections. Additionally, our study suggests that all siblings should undergo a screening for VUR, even in the absence of UTI. DMSA scintigraphy of asymptomatic siblings appears to be beneficial in preventing renal injury.

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