VESICOURETERAL REFLUX SCREENING IN SIBLINGS OF PATIENTS WITH KNOWN REFLUX

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Abstract-The prevalence of vesicoureteral reflux (VUR) among siblings of children with VUR has been reported to be from 4.7% to 51%. The incidence of VUR in the general population is less than 1% but it is high in risk groups. In a prospective study we started identifying the incidence and severity of VUR and renal parenchymal lesions in the siblings of patients known to have urinary tract infection (UTI) with reflux. Between October 1994 and February 2002, 31 siblings of 26 index patients were screened with direct voiding cystography. Technetium -99^{m} dimercaptosuccinic acid (DMSA) nuclear renal scans were performed in siblings with VUR to detect renal scarring. The cystograms were interpreted as showing the presence or absence of VUR and the DMSA scan as symmetrical or asymmetrical differential function, with or without renal scar. Sixteen of 31 siblings were found to have vesicoureteral reflux representing an incidence of 51.61%. Mean age at presentation of the 8 boys and 23 girls was 2.5 years (range 6 months to 12 years). The majority of them were asymptomatic. Reflux was unilateral in 11 siblings and bilateral in 5. Of 16 siblings with reflux, 6 (37.5%) had a history of symptomatic UTI. The frequency of VUR was equal in siblings over 6 years and those younger. Fifteen of the 16 siblings with VUR had DMSA scintigraphy, of whom 5 were normal and 10 (66.66%) showed abnormalities (nine asymmetrical differential function and one parenchymal defect), which was bilateral in 7 and unilateral in 3. This study confirms a significant overall incidence of VUR in the siblings of patients with known reflux. The prevalence of reflux in older siblings is similar to those in the younger ones. The high rate of reflux in this population, especially girls, over 6 year old might be attributed to bladder dysfunction.

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Key Words: Vesicoureteral reflux, Sibling, renal scarring, children

INTRODUCTION

The primary vesicoureteral reflux (VUR) is the most common anomaly present in children with urinary tract infection (UTI). The association of vesicoureteral reflux, UTI and renal damage is well known in 30-60% of children (1,2). The hereditary and familial nature of VUR is now well recognized (3). The true incidence of VUR in asymptomatic children is less than 1% (4) but it is high in at risk groups (5-9). The prevalence of VUR among siblings of patients with VUR has been reported to be from 4.7% to 51% (5,10-12,18). VUR has been reported in asymptomatic and symptomatic siblings potentially leading to UTI, renal damage, hypertension or chronic renal failure (13-15). The incidence of renal damage in the siblings of patients with primary VUR is estimated at 4.7-41% (13,14,21). The course of VUR is asymptomatic in most children. UTI may be the only sign that a child is at risk for VUR. High-grade reflux is associated with 8 to 10 times more scarring compared with when reflux is absent and 4-6 times more scarring compared with when only low-grade reflux is found (22). The early detection of VUR allows prophylactic antibiotic treatment or early reimplantation of the ureter, before UTI occurs, and may prevent the development of renal scarring. Identification of VUR in general population is not feasible but it would seem important to investigate groups at risk by voiding cystography or cystosonography (23-25) before the first urinary tract infection. The purpose of this prospective clinical study was to determine the age related incidence and severity of VUR in siblings of patients with known reflux to assess the use of screening at different ages.

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MATERIALS AND METHODS

From October 1994 through February 2002, we prospectively screened 31 siblings of 26 eligible index

patients with an awake voiding cystourethrogram (VCUG) or direct radionuclide cystography (RNC) regardless of the presence of symptoms or history of documented UTI. A group of 31 siblings (21 with one sibling and five families with two siblings) was evaluated. All children within this group had primary reflux. Siblings with structural abnormalities such as neurogenic bladder, posterior urethral valves, ureteroceles or other congenital anomalies were excluded from consideration. In the early phase of study 99^{m} Tc-DMSA renal cortical scintigraphy was performed in siblings with VUR. The intravenously injected activity was adjusted to the patient's weight, according to a standard schedule (26). Three hours after injection with 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 to 55% of the total renal activity was considered as normal (symmetrical renal split function). The renal scintigraphic patterns were independently interpreted by two senior nuclear medicine staff; a kidney with regular shape and a tracer uptake which appeared to be homogenous was considered as normal. Single or multiple cortical defects and, focal or diffuse photopenic patterns in one kidney were considered as abnormal (27-29). The cystograms were obtained with either radiographic technique with iodinated contrast medium or with direct radionuclide technique. The reflux demonstrated by radionuclide technique was graded as mild-reflux of tracer in the ureter only, moderate-reflux of tracer in the renal pelvis which may have appeared minimally dilated or severe-reflux of tracer in a grossly dilated renal pelvis (30). For purposes of comparison, radiographic grades I and II were classified as mild, grade III and IV as moderate, and grade V as severe (18,31). Cases of bilateral reflux in which the grade differed on each side were assigned the grade of the more severely affected side. The radiographic cystograms were evaluated for the presence and grade of reflux in accordance with the international grading system (4). When VUR was diagnosed, antibiotic prophylaxis was started in a single daily dose given at night time, including those without prior symptoms or known urinary tract infection. All siblings underwent ultrasonography (US) by a pediatric radiologist. The kidneys were studied by sonography for size, shape, parenchymal echogenicity, corticomedullary differentiation, irregularrity of the kidney outlining and parenchymal reduction. Reflux was considered to have resolved when a follow up radionuclide cystogram demonstrated no reflux. In addition to recording reflux resolution, any change relative to reflux grade at diagnosis was noted. The chi-square procedure was used to determine the statistical significance of the relationships between variables. P value below 0.05 was considered statistically significant. Before starting the investigation the nature, aim, potential risks and benefit of cystourethrography and DMSA scan were explained and oral informed consent was obtained from the parents or guardians. The study was approved by the ethics Committee of Tehran University of Medical Sciences.

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RESULTS

Thirty one siblings of the 26 index patients were studied. Four index patients were male and the remaining 22 were female. The age of the index patients ranged from 6 month to 12 years (mean 4 years 8 months). Reflux was bilateral in 11 (41.53%) and unilateral in 15 (58.47%) of the index patients. In the group with unilateral reflux, all 15 patients had mild or moderate reflux. In the group with bilateral reflux 2 out of 11 (18.17%) patients had severe reflux (Table. 1).

Table 1. The relationship between the severity of VUR and laterality in 26 index patients

Grade of VUR	Unilateral	Reflux	Bilateral	Reflux
	n	%	n	%
Mild (I, II)	7	(70)	3	(30)
Moderate (III, IV)	8	(57)	6	(43)
Severe (V)	0	---	2	(100)
Total	15	(58)	11	(42)

The siblings group consisted of 8 boys and 23 girls. Sixteen of 31 siblings were found to have vesicoureteral reflux representing an incidence of 51.61%. Eleven siblings had unilateral reflux and 5 had bilateral reflux, thus 21 of 32 (65.62%) renal units had VUR. Reflux occurred with nearly equal frequency on each side (Table 2). Reflux was mild in 9 (56.25%), moderate in 6 (37.5%) and severe in 1 (6.25%) sibling. In the group with unilateral reflux, all 11 siblings had mild or moderate reflux. In the group with bilateral reflux only 1 (32.2%) patient had severe reflux (Table 3). The majority of siblings were asymptomatic, as shown in table 4. Of the siblings with VUR, 13 (81.25%) had normal kidneys on sonograms and parenchymal scarring was evident in 3 (18.75%). When grouped according to age, siblings 7-

12 years old had an equal frequency of reflux with the children less than 6 years. Table 5 shows the comparison between the incidence of VUR in this study and other previous investigations.

Table 2. Reflux status in 31 siblings according to laterality

Laterality of reflux	Siblings	
	n	%
None	14	46.6
Unilateral		
Right	5	16.7
Left	6	20
Bilateral	5	16.7
Total	30	100

Table 3. The relationship between the severity of VUR and laterality in16 siblings with VUR

Grade of VUR	Unilateral	Bilateral	Total	
	n	n	n	%
Mild (I,II)	7	2	9	56
Moderate (III,IV)	4	2	6	37.5
Severe (V)	0	1	1	6.5
Total	11 (68.8%)	5 (32.2%)	16	(100)

Table 4. Number and percent of 16 siblings with vesicoureteral reflux according to previous history of UTI

Previous history of UTI	n	%
Positive	6	37.5
Negative	10	62.5
Total	16	100

Table 5. Result of siblings screening with voiding cystourethrogram

Reference	Subjects (n)	Reflux (%)
Peeden and Noe (10)	24	46
Parekh et al. (12)	78	51
Noe et al. (15)	354	34
Wan et al. (19)	452	24
Kenda and Zupancic (20)	53	42
Present Series	31	51.61

Of the 16 siblings with reflux, DMSA was abnormal in 10 of 15 patients (17 of 30 refluxing renal units or 60.66%, P<0.005). Of these cases, 7 (70%) were asymptomatic and had no history of UTI. Five had normal DMSA and one sibling refused DMSA scintigraphy (Fig. 1). When siblings were grouped according to kidney units, scintigraphy showed renal abnormalities in 8 (50%) of the 16 renal units with grade I or II, 7 (58.33%) of the 12 with grade III or IV and both (100%) of the 2 renal units with grade V disease (Fig. 2). Of the 10 siblings with renal parenchymal abnormalities 7 (70%) were asymptomatic and had no history of UTI. Of the 15 siblings with VUR who had both renal cortical scintigraphy and renal ultrasonography, DMSA and US findings were abnormal in 10 (66.66%) and 3 (20%) of the siblings respectively. Treatment consisted of prophylactic antibiotics in all siblings with reflux. A mean follow up of 26 months (range 1 month to 84 months) was available in 15 (93.75%) patients. Vesicoureteral reflux resolved in 8 (50%) patients, 2 (12.5%) underwent an anti-reflux procedure and 6 (37.5%) are still being observed on antibacterial prophylaxis with a reasonable expectation of spontaneous cessation of the reflux**.**

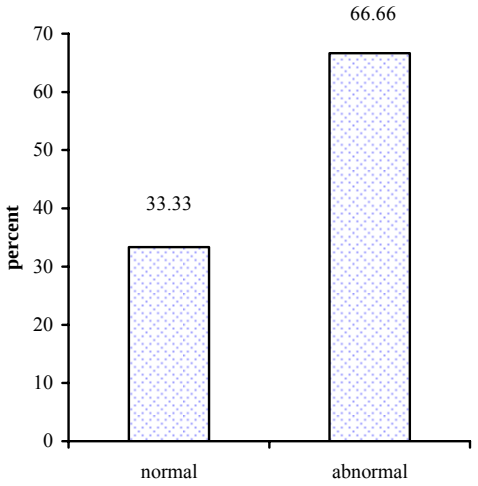

Fig. 1. Frequency of DMSA abnormality in 15 siblings with vesicoureteral reflux

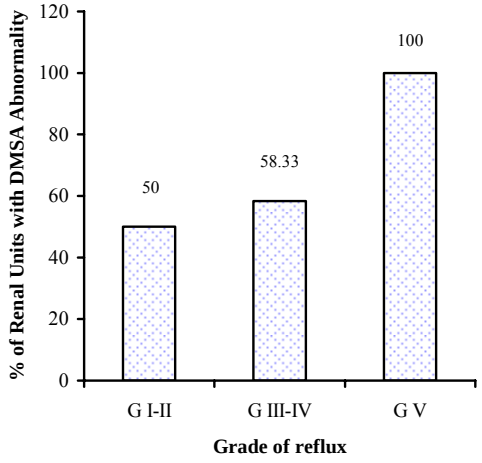

Fig. 2. Correlation of 99^{m} Tc-DMSA renal scintigraphy abnormalities with reflux grade (P < 0.005)

DISCUSSION

The occurrence of VUR in the siblings of patients with reflux has been established by other series (16,17,21). Reflux nephropathy is the cause of end stage renal disease in 3% to 25% of children and 10% to 15% of adults (14,15,17). As a preventable cause of renal damage, the benefits of early detection and treatment are clear (8,30,32). The debate on VUR is now focusing more on early detection rather than on management (8). Screening for reflux has been recommended in recognized at risk groups such as children with UTI (5), first degree relatives of children with reflux (6), schoolgirls with covert bacteriuria (7), infants with antenatal hydronephrosis (8) and patients with multicystic dysplastic kidney (9). We analyzed familial occurrence of primary VUR, examining siblings of the affected patients-31 individuals: 23 sisters and 8 brothers. VUR was present in 16 siblings, which makes 51.61% of the examined subjects. The result obtained is significantly higher than that reported by numerous authors in the literature (5,11,12,17,18). Patient age has been shown to be one of the factors primarily affecting the incidence of VUR. In the analyzed materials, we divided the siblings into two groups aged 0-6 years and over the age of 6. We wanted to evaluate the relationship between the incidence of reflux and siblings' age. Most authors show such a correlation. They address that, siblings over 5-7 years old suffer from reflux considerably less often (13,19). In our study, 50% of siblings either under 6 years of age or older had VUR. This prevalence in siblings younger than 6 years old is similar to that reported by other authors (10-12); but in contrast to previously reported studies, the incidence of VUR in siblings over 6 years was significantly elevated (11,13,19). Noe, though, recognized reflux in 28% of the examined siblings older than 6 years compared to 32% of the examined cases younger than 3 years of age (33).

In some patients, VUR is related only to reduction of the submucous segment of the ureter (34), whereas some cases of VUR diagnosed in older female patients seem to be secondary to bladder dysfunction (35). Of 8 siblings aged >6 years, 6 (75%) were female. However, we did not find any clear reason for high incidence of reflux. The high rate of reflux in this population might be attributed to bladder dysfunction, presumably due to cultural factors. We found the presence of asymptomatic reflux in 62.5% of the siblings with VUR. Noe present similar results (17). Nine (56.25%) of our siblings had low grade reflux (range I to II), while 6 had III to V (37.5%). Only one (6.25%) sibling had severe (grade V) reflux .These numbers are consistent with the reports published by other authors (12,13,19). In the siblings of index patients with VUR, it was observed that reflux tended to be diagnosed more frequently in females than in males. In our study the incidence of reflux was significantly higher in females (85.5%) compared to males (14.28%). These results are similar to those reported by other series (12). It seems that it results from widely recognized predisposition of the female sex to higher prevalence of the anomaly (17,19). In contrast, Pore et al. did not find a different incidence between affected boys and girls (13). The incidence of renal damage and scarring in siblings of patients with VUR has been reported from 4.7% to as high as 41 % (13,14,21). These values are the incidence of parenchymal damage in siblings with reflux and not the whole sibling population. In present study most of siblings who underwent scintigraphy had abnormal DMSA scan. These results are higher than that reported by numerous authors (13,21).

US was abnormal in 18.75% of siblings compared with 66.66% of patients with abnormal DMSA, while no positive US examinations were found in patients with normal DMSA scans. It confirms the opinion of numerous authors that ultrasound examination is not a sufficient diagnostic method (37). In conclusions, this study confirms a significant overall incidence of VUR (51.61%) in the siblings of patients with known reflux. Grade of reflux is low in the majority of siblings. The prevalence of reflux in older siblings is similar to those who are young. The high rate of reflux in this population, especially girls over 6 years old might be attributed to bladder dysfunction. Simultaneous urodynamic studies and cystography may be helpful for delineating the association of bladder pressure with reflux. Additionally, this study did not confirm the conventional view that only siblings less than 5 years old suffer from reflux. We believe that all siblings aged $\leq$ 12 years should undergo voiding cystourethrography.

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