Familial vesicoureteral reflux in asymptomatic siblings

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SUMMARY: Çelik A, Ulman İ, Aydın M, Arıkan A, Avanoğlu A, Gökdemir A. Familial vesicoureteral reflux in asymptomatic siblings. Turk J Pediatr 2002; 44: 240-243.

A prospective study was established to identify the incidence of vesicoureteral reflux in the asymptomatic siblings of patients with reflux in our region. Of 32 patients with reflux, 37 siblings were screened with urine analysis, urine culture and contrast voiding cystourethrograms, and six (16.2%) were found to have reflux. Renal scan revealed scarring in five. We concluded that siblings of children with vesicoureteral reflux are at high risk, and must be screened so that renal damage and associated morbidity secondary to reflux might be minimized.

Key words: vesicoureteral reflux, sibling relations, hereditary diseases.

Primary vesicoureteral reflux (VUR) is the most common urological anomaly in children[1-3]. Reflux nephropathy is the cause of end stage renal failure in 3-25% of children and in 10-15% of adult patients[3-11]. Incidence of VUR is less than 1% in the general population[2,12,13]. Familial tendency of VUR detected in twins was first described by Stephens in 1955[14]. Studies performed in recent years found the incidence of VUR in siblings between 8-46%[1-3,8,15-17]. Screening of siblings for reflux has become a well accepted practice in many developed centers. Since the role of familial characteristics of reflux is known, racial differences may be present. There is not sufficient data in the literature about sibling reflux among Turkish children apart from the study of Şahin et al.[18]. A prospective study was designed to find the incidence of VUR in asymptomatic siblings of index patients with VUR in our region.

Material and Methods

With parental consent, siblings of the index patients, having no previous urological symptoms, were evaluated with routine urine analysis, urine culture and contrast voiding cystourethrograms (VCUG). Siblings positive for reflux at the end of these investigations were managed as patients with primary VUR. Siblings and patients with neurogenic bladder, posterior urethral valve, ureterocele or other congenital anomalies causing secondary reflux were not included in the study.

Results

Thirty-seven siblings (16 female/21 male) of 32 patients were studied (Table I). The ages of patients ranged from 18 months to 16 years (mean, 7.9 years). There were no previous urological symptoms in any of the siblings, and none of the families had a history of other members with VUR.

Urine analysis revealed pyuria in two siblings. One of these had unilateral low-grade (I°) reflux accompanying bilateral incomplete duplex systems. The other sibling with infection cultured E. coli, and this four-years-old male had unilateral renal scar without detectable

Table I. Sex and age distribution of siblings

Age (year)	F	M	Total
<1	–	–	–
1-2	–	2	2
3-5	2	6	8
6-10	9	10	19
>10	5	3	8
Total	16	21	37

F: female, M: male

Table II. Findings in asymptomatic siblings

	Age (year)	Sex	VCUG (side/grade)	USG	DMSA (scar)	Management	Follow-up
1♦	4	M	–	Normal	R+	conservative	w/o symptoms
2	6	M	L/2	Normal	–	conservative	VUR disappeared
3*	6	F	R/1	Normal	–	conservative	VUR disappeared
4	7	M	L/4	Left pelvicaliectasis	L+	UNS	VUR disappeared
5	9	F	L/5	Left pelvicaliectasis	L+	UNS	VUR disappeared
6	10	F	R/3	Normal	R+	UNS	VUR disappeared

VUR: vesicoureteral reflux; VCUG: voiding cystourethrogram; M: male; F: female; R: right; L: left; Bil: bilateral; UNS: ureteroneocystostomy; USG: ultrasonography.

♦ DMSA renal scan revealed scarring on the right but no detectable reflux was found.

* Bilateral incomplete duplication was detected.

reflux. VUR was noted in six siblings (16.2%) with an equal sex distribution (3M/3F). Reflux was grade I to II in two siblings. Grade III to V reflux was present in four patients, and one of them was bilateral. DMSA renal scan revealed reflux nephropathy in the latter four siblings, and all were treated surgically. The former two siblings with low-grade reflux were followed conservatively, and reflux resolved in both. All siblings with VUR were followed up without further deterioration (Table II).

Discussion

Vesicoureteral reflux is a common abnormality seen in children with urinary tract infections. Reflux of the infected urine to the upper tract may cause renal scarring and nephropathy. Unless treated promptly, 30-60% of patients with VUR have radiographic evidence of renal scarring[19], and hypertension develops in 11-20%. Twenty percent of renal transplantations are done in patients with reflux nephropathy[20]. At present, 40% of children on hemodialysis are cases that have end stage renal failure due to reflux nephropathy. Noe et al.[6] detected VUR in as many as 66% of children whose mothers had VUR previously. Succeeding reports instituted a familial aspect of vesicoureteric reflux disease. Puri et al.[3] reported the incidence of reflux as 13.6% in 624 siblings with much higher grade and reflux nephropathy incidence. Because of high incidences of both VUR and renal scarring at the time of diagnosis, early evaluation has been suggested in siblings of index patients[2]. The incidence of reflux and associated findings in our study group were high so as to support the present data in the literature.

There is a familial tendency or trait in the etiology of VUR, although special features of inheritance are still controversial. Some investigators proposed an autosomal dominant type of inheritance[21]. Sengar et al.[22] suggested a linkage with the major HLA complex located on the sixth pair of human chromosomes. Middleton et al.[23] proposed that it was sex linked. Others suggest polygenic type of inheritance[1,24,25]. Eccles et al.[26] presented evidence that this common disorder may be caused by mutations in the developmental pathway of which the PAX2 gene forms a part, but this is not a major cause of primary familial reflux[27]. Further investigations are required for clear explanation of inheritance of reflux.

The likelihood of reflux resolution, especially in siblings of index patients, has been reported to be around 58%, and this possibility is 28% per year[9,11,12]. Kenda et al.[2] reported VUR incidence as 50% in siblings under one year old, and it is 9% in patients over two years of age. The resolution of reflux with conservative treatment was somewhat low in our series. However, the ages of the patients with persistent reflux were between 7 and 14, whereas two siblings at six years of age were devoid of reflux after a period of conservative treatment. Nevertheless, the reflux grades of these cases might have also affected the spontaneous resolution chance, as they were lower compared to those of nonresponders to conservative follow-up. It is not possible to suggest a unique behavior for the reflux in siblings looking at the results of this relatively small series, but such a difference was not defined in the published studies either.

In previously reported studies, the incidence of reflux between male and female siblings was similar, except for Noe's report[4], in which there was a higher incidence in females. In the present study, there was also no correlation or similarity between reflux grades, sex distribution, or renal scarring, when index patients were compared to siblings with reflux.

In a four-year-old sibling in our series, DMSA renogram detected scarring in the absence of reflux. This situation suggests a possible spontaneous resolution of an asymptomatic reflux and unrecognized infection in the course. Reflux may resolve spontaneously if patients can be prevented from infection, as a result of long-term follow-up. But being unaware of ongoing reflux puts the patient at risk for an unexpected, and at times undiagnosed, pyelonephritis. Noe proposed that VCUG should be performed in all female and male siblings up to three years of age, because of higher incidence of VUR in this group, and in all female and male siblings between 3 to 5 years of age who have a history of urinary tract infection. Ultrasonography may be sufficient in asymptomatic male siblings over three years, and in female siblings over five years of age[4].

One of the main concerns related to routine sibling screening is the unavailability of a single reliable, noninvasive, and readily performed test. Indirect radionuclide cystography is a good alternative for VCUG, but only in children over five years of age[2,5,10,16]. Despite its disadvantages, VCUG is still the screening test of choice for most siblings. Nevertheless, a single DMSA scan in siblings over five years of age may suffice for screening purposes. A normal result can rule out complicated reflux reliably in most cases. Positive findings will indicate further evaluation including cystography.

In conclusion, detection and management of siblings for VUR is of vital importance due to the high incidence of renal damaging. Asymptomatic siblings may have previously undetected renal scars either with or without reflux. In this respect, families of children with VUR should be told about its familial trait. All asymptomatic siblings should be first evaluated by urine sampling, urine culture, urinary ultrasonography and contrast VCUG regardless of age or sex. Symptomatic siblings should be evaluated as a patient and contrast VCUG should be done, followed by a DMSA renal scan.

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