

Renal Cortical Abnormalities in Siblings of Index Patients With Vesicoureteral Reflux

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KEY WORDS

vesicoureteral reflux, familial VUR, screening, siblings

ABBREVIATIONS

DMSA—dimercapto-succinic acid

UTI—urinary tract infection

VCUG—voiding cystourethrogram

VUR—vesicoureteral reflux

Dr Hunziker carried out the initial analyses and drafted the initial manuscript; Dr Colhoun reviewed the radiological data; Professor Puri conceptualized and designed the study, supervised data collection, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-3498

doi:10.1542/peds.2013-3498

Accepted for publication Jan 3, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.



WHAT'S KNOWN ON THIS SUBJECT: The familial nature of vesicoureteral reflux (VUR) is well recognized. Several studies have shown that siblings of children with VUR are at much higher risk for reflux than the general pediatric population with a reported prevalence between 26% and 50%.



WHAT THIS STUDY ADDS: There is increased risk of renal cortical abnormalities in siblings with a previous urinary tract infection, siblings with high-grade VUR, and siblings >1 year of age. This information may be useful when counseling parents about the risk of familial VUR.

abstract

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OBJECTIVE: Screening siblings of index patients with vesicoureteral reflux (VUR) has been proposed to identify children who are at risk for renal damage. However, screening siblings for VUR remains controversial. We investigated the prevalence of VUR and renal cortical abnormalities in the sibling population in a large cohort of families with VUR.

METHODS: Between 1998 and 2012, parents of index patients with grade III to V VUR were asked permission to screen siblings <6 years of age for VUR. Siblings were divided into 2 groups: siblings with a documented history of a previous urinary tract infection (UTI) and siblings who were screened for VUR and never had a UTI. A logistic regression model was used to determine independent risk factors associated with renal cortical abnormalities such as history of presentation, age, gender, and grade of VUR.

RESULTS: There were 318 siblings in 275 families in the study. VUR was found after screening in 190 (60%) siblings and after a UTI in 128 (40%). Multivariate analysis revealed that siblings who had a previous UTI (odds ratio: 3.38), siblings with high grade reflux (odds ratio: 3.62), and siblings over 1 year of age (odds ratio: 2.84) were the most significant independent risk factors associated with renal cortical abnormalities.

CONCLUSIONS: There is increased risk of renal cortical abnormalities in siblings with a previous UTI, siblings with high-grade VUR, and siblings over age 1 year. This information may help to counsel parents about the risk of VUR and reflux nephropathy in familial VUR. *Pediatrics* 2014;133:e933–e937

Vesicoureteral reflux (VUR) is the most common disease of the urinary tract in children,¹ occurring in 1% to 2% of the pediatric population and in 30% to 40% of children presenting with a urinary tract infection (UTI).^{2,3} The familial nature of VUR is well recognized. Several studies have shown that siblings of children with VUR are at much higher risk for reflux than the general pediatric population with a reported prevalence between 26% and 50%.⁴⁻⁶ However, because VUR can resolve spontaneously with age,^{7,8} it is difficult to accurately determine the exact prevalence in family members.

One of the main goals of treating the child with VUR is prevention of recurring febrile UTIs and minimizing risk of renal damage and long-term renal impairment. Renal parenchymal damage can be congenital (hypoplasia or dysplasia) or acquired scarring. Acquired scarring results from pyelonephritis induced renal injury,⁹ whereas congenital reflux nephropathy is a result of abnormal embryological development with subsequent renal dysplasia. Exposure to UTIs in patients with congenital renal dysplasia can lead to progression of renal parenchymal damage. Reflux associated nephropathy is an important cause of hypertension and end-stage renal disease.⁸⁻¹¹ The recent UK renal registry report revealed that renal dysplasia and VUR remained the commonest condition causing end-stage renal disease in children <16 years of age (32%). Furthermore, renal scarring was the main cause of hypertension accounting for 34% of the children <16 years of age.¹²

Screening siblings of index patients with VUR has been proposed to detect a population at risk, potentially allowing treatment to prevent acute illness and decrease adverse outcomes associated with VUR, including UTIs, pyelonephritis, and renal injury.¹³ However,

screening of asymptomatic siblings and offspring of refluxing parents is controversial.¹⁴ Although some clinicians believe that early identification of children with VUR may prevent episodes of UTIs and associated renal scarring, others think that screening asymptomatic individuals is likely to result in overtreatment of clinically insignificant VUR.¹⁴

We analyzed data on a large cohort of familial VUR from a single institution in whom imaging studies were systematically performed. This study provides important information regarding epidemiologic data on gender, age, grade distribution, and renal functional abnormalities. We further define the risk factors associated with renal functional abnormalities in the siblings with VUR.

METHODS

Institutional review board approval (RP347) was received in 1998 to prospectively screen siblings of index patients with high-grade VUR at our institution, and data of 275 families were recorded until December 2012. Parents of index patients with grade III to V VUR were asked permission to screen siblings who were aged <6 years; written informed consent was obtained from the parents of the participants after they were informed of the aims, potential risks, and benefits

of imaging studies. Families with ≥ 2 siblings with any grade of VUR were included in the analysis. Index patients were diagnosed after a documented UTI. A UTI was diagnosed when the results of a urine culture showed a bacterial count $>10^5$ and grew a single organism. Siblings were divided into those diagnosed after a documented UTI and those diagnosed after screening. Reflux was confirmed in all index patients and siblings by voiding cystourethrogram (VCUG) and graded according to the International Classification Systems.¹⁵ We excluded 2 patients with VUR secondary to neurogenic bladder and 1 patient with posterior urethral valves from the study.

We enrolled 275 families with a total of 593 children with VUR, including 239 (40%) boys and 354 (60%) girls, in this study. The number of families with 2, 3, 4, and 5 siblings was 237, 34, 3, and 1 respectively. Four hundred twenty-four siblings were screened, and 190 (45%) siblings were found to have VUR. In addition, 128 siblings were diagnosed with VUR after a UTI. Details of the demographics of the 275 index patients and the 318 siblings are summarized in Table 1.

Mean \pm SD age was 2.71 ± 2.41 in index patients and 1.98 ± 2.19 in siblings. Index patients were significantly older compared with siblings ($P < .001$).

TABLE 1 Demographics of 275 Index Patients and 318 Siblings With VUR

	Index Patients (n = 275)	Siblings With UTI (n = 128)	Siblings Screened (n = 190)
Gender			
Female	165	80	109
Male	110	48	81
Age, y			
Mean age (mean \pm SD)	2.71 \pm 2.41	2.54 \pm 2.35	1.61 \pm 2.01
<1	108	55	119
>1	167	73	71
Grade of VUR			
I	—	6	7
II	—	8	9
III	137	59	82
IV	107	50	82
V	31	5	10

Gender and grade of VUR were not different between siblings and index patients.

In index patients and in siblings, renal functional abnormalities were evaluated by dimercapto-succinic acid (DMSA) scintigraphy. DMSA scans were performed in 231 index patients (84%) and in 248 siblings (78%). Renal scintigraphy was carried out after intravenous injection of ^{99m}Tc -DMSA. Fractional right and left renal activity was calculated in each kidney after background correction. A kidney uptake of 45% to 55% of total renal activity was considered normal. Renal functional abnormalities were classified into 3 patterns: mild (focal defects in uptake between 40% and 45%), moderate (uptake of renal radionuclide between 20% and 40%), and severe (shrunken kidney with relative uptake <20%). In children presenting with a UTI, DMSA scans were performed at least 6 months after the first UTI.

Differences in gender, age, grade of VUR, and renal functional abnormalities between siblings and index patients were assessed. In addition, differences between screened siblings and siblings with a previous UTI were evaluated. To analyze the impact of age, children were further divided into those who were aged <1 year and those who were between 1 and 6 years old.

For statistical analysis χ^2 test or Mann Whitney *U* test was used when appropriate. Univariate and multivariate logistic regression analysis was performed to identify the risk factors of renal functional abnormalities in siblings with VUR. In cases of bilateral

VUR, the higher grade of VUR was assigned for the regression analysis. All covariates that were significant on univariate analysis were included in a multivariate regression model with statistical significance considered at $P < .05$.

RESULTS

Of the 318 siblings with VUR, 189 (59%) were girls and 129 (41%) were boys. There were 174 (55%) siblings <1 year of age, and 144 (45%) were 1 to 6 years old. Screened siblings were diagnosed at a younger age compared with siblings who had a previous UTI ($P < .001$). Of siblings <1 year of age, 80 (46%) were boys and 94 (54%) were girls, whereas of siblings >1 year of age, 49 (34%) were boys and 95 (66%) were girls. In siblings VUR was usually of high grade, with grade IV to V VUR being detected in 147 (46%) siblings. Gender and grade of VUR were not different between siblings who were screened and siblings who had a documented UTI before diagnosis of VUR.

DMSA scans were performed in 231 index patients and in 248 siblings. Table 2 shows mild, moderate, and severe renal functional abnormalities in index patients, siblings with a previous UTI, and siblings who were screened. The prevalence of renal functional abnormalities was significantly more common in index patients compared with siblings (86 [37%] vs 57 [23%], $P = .001$). Siblings with renal functional abnormalities had grade III to V VUR, except 1 sibling with mild scarring who had grade II VUR. Renal functional abnormalities were seen in 34% of siblings

who were diagnosed with VUR after a UTI compared with 15% in siblings who were diagnosed with VUR after screening ($P = .001$).

In siblings univariate analysis revealed that those who had a previous UTI ($P = .001$), siblings with high-grade reflux ($P = .010$), and siblings >1 year of age ($P = .044$) were significant risk factors associated with renal functional abnormalities. Multivariate analysis showed that siblings who had a previous UTI ($P < .001$), siblings with high-grade reflux ($P = .002$), and siblings >1 year of age ($P = .009$) were the most significant independent risk factors associated with renal functional abnormalities (Table 3).

DISCUSSION

The familial nature of VUR is well known. Because many children with VUR have no symptoms of UTI and invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of familial VUR is unknown.¹⁴ The prevalence of VUR determined from a recent meta-analysis was 27.4 (2.9–51.9) per 100 siblings screened and 35.7 (21.2–61.4) per 100 offspring screened.¹⁵ Our study revealed that 45% of screened siblings without previous UTI have VUR. Similar, Noe et al investigated 354 siblings of 275 index patients and found 119 (34%) with VUR, including 75% asymptomatic siblings.⁴ It is well known that the

TABLE 2 Renal Functional Abnormalities in Familial VUR

	Index Patients (<i>n</i> = 231)	Siblings With UTI (<i>n</i> = 102)	Siblings Screened (<i>n</i> = 146)
Mild renal functional abnormalities	33	21	7
Moderate renal functional abnormalities	38	10	12
Severe renal functional abnormalities	15	4	3
Total	86 (37%)	35 (34%)	22 (15%)

TABLE 3 Regression Analysis for Predictors of Renal Functional Abnormalities in Siblings With VUR

	OR (95% CI)
Univariate analysis	
Siblings with a previous UTI	2.94 (1.60–5.42)
Grade IV–V VUR	2.83 (1.28–6.23)
Siblings >1 y	2.16 (1.02–4.43)
Male gender	0.55 (0.28–1.15)
Multivariate analysis	
Siblings with a previous UTI	3.38 (1.44–8.46)
Grade IV–V VUR	3.62 (1.58–8.29)
Siblings >1 y	2.84 (1.30–6.19)

CI, confidence interval; OR, odds ratio.

prevalence of VUR decreases with age. Our study revealed that screened siblings were younger compared with siblings who had a previous UTI. The higher rate of prevalence of VUR in our asymptomatic siblings compared with other studies may be explained by the younger age of our screened siblings. The ultimate aim in the management of childhood VUR is prevention of permanent renal damage by minimizing the risk of recurrent febrile UTIs. It is well known that children with UTI and VUR are at increased risk for pyelonephritis. Children with VUR and UTI are nearly 4 times more likely to have a renal scar in refluxing units than those with pyelonephritis and no reflux.^{13,16} Risk factors for renal functional abnormalities in siblings were associated with a history of a previous UTI, high-grade VUR, and age >1 year. Our study showed that the prevalence of renal damage in screened siblings without previous UTI was 15%, whereas it was 34% in siblings with a previous UTI. Although the incidence of renal functional abnormalities was significantly lower in screened siblings compared with symptomatic siblings, two-thirds of the screened siblings with renal function abnormalities had moderate to severe abnormalities. Because the vast majority of screened siblings were aged <1 year, these abnormalities were most likely congenital dysplasia. The observed higher incidence of renal cortical abnormalities in siblings after

a UTI compared with screened siblings confirms the potential risk of UTI associated renal cortical injury. Furthermore, the prevalence of renal functional abnormalities was highest in older siblings and lowest in younger siblings. These older siblings may have had unrecognized recurrent UTIs leading to renal scar formation or persistent VUR and renal cortical abnormalities.

Although some studies have shown that lower grades of VUR are observed in siblings who are screened for VUR, our study clearly showed that the vast majority of siblings, whether symptomatic or asymptomatic, have intermediate to high-grade VUR. Of the siblings with VUR, >90% had grade III to V VUR, with 46% of siblings having grade IV or V VUR. The higher rate of grade IV and V VUR in our sibling population could be explained by the younger age of our siblings with 55% being under the age of 1 year.

With the increased evidence that VUR has a high frequency among family members, the updated American Urological Association Pediatric Vesicoureteral Reflux Guidelines included recommendation for familial VUR.^{13,17} To establish guidelines, data from 22 articles published between 1975 and 2008, including 2957 siblings and 244 offspring, were analyzed. However, the lack of prospective studies for screened siblings to assess clinical health and outcomes made evidence-based guideline

recommendation difficult. The American Urological Association panel recommends a VCUG in siblings of children with VUR if there is evidence of renal cortical abnormalities or renal size asymmetry on ultrasound or if there is a history of UTI in the sibling who has not been tested. In addition, it is recommended that families should be informed about the increased likelihood of another family member having VUR; furthermore, the long-term concerns of hypertension and renal functional loss should be outlined.

Our study investigating renal functional abnormalities in a large cohort of siblings with VUR makes a clear distinction between symptomatic and asymptomatic siblings with VUR. In siblings with VUR identified through screening without any past history of UTI, the likelihood of renal functional abnormalities was significantly lower compared with siblings with a previous UTI ($P < .001$). Increased prevalence of renal functional abnormalities in symptomatic siblings indicates that parents and health providers should be aware of the increased risk of pyelonephritis and renal cortical abnormalities in siblings diagnosed with VUR after a UTI. Because screening of asymptomatic siblings of index patients with VUR is still controversial, it is important at least to counsel parents regarding prompt treatment of acute UTI and subsequent VCUG in siblings of children with VUR.

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DOI: 10.1542/peds.2013-3498 originally published online March 24, 2014;

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