



Renal Scarring in Children with Primary Vesicoureteral Reflux Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Author KK designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors RRM and WAW managed the analysis of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the incidence of renal scarring among patients with primary vesicoureteral reflux (VUR) and the possible risk factor(s), we studied 69 children (42 girls and 27 boys) with VUR attending the Pediatric opd.

Study Design: Prospective Observational study.

Place and duration of Study: Department of pediatrics, Sher I Kashmir Institute of Medical Sciences, Srinagar, Kashmir between June 2017 to June 2018.

Methodology: All the patients were assessed for VUR grade by voiding cystoureterography and for presence of renal scarring by (99 m) technetium dimercapto–succinic acid scintigraphy.

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Results: Grade of reflux and number of urinary tract infection (UTI) episodes (≥ 3) were found to be statistically significant risk factors for renal scarring ($P < 0.05$). However, there was no significant association with gender, familial history and laterality of the disease ($P > 0.05$). Similarly, there was no statistically significant difference of frequency of renal scarring among the different age groups ($P > 0.05$).

Conclusions: It was concluded that recurrences of UTI and VUR severity are significant risk factors for renal scarring in children with VUR. Therefore, identification of VUR at an early age may offer the opportunity to prevent episodes of UTI and possible formation of renal scars that may result in end-stage renal failure.

Keywords: Vesicoureteral reflux; voiding cystourethrography; dimercapto-succinic acid scintigraphy; renal scarring.

1. INTRODUCTION

Urinary tract infection (UTI) is the most common serious bacterial infection in young children. Up to 8.4% of girls and 1.7% of boys will have a UTI in the first 6 years of life [1]. UTIs cause short-term morbidity such as fever, dysuria, and pain and may also result in permanent kidney scarring [2–5]. Many factors, such as age, gender, race, and circumcision status, are believed to increase the risk of recurrent UTI [6–8], but over the last few decades, no factor has received more attention than vesicoureteral reflux (VUR). Vesicoureteral reflux (VUR) is one of the most common congenital urinary tract abnormalities diagnosed in childhood. The reported prevalence is about 1%, although some believe that it may actually be higher [9]. VUR is believed to predispose to urinary tract infection (UTI) and renal scarring. UTI is the most common factor associated with VUR, and it is a pre-requisite for formation of further renal parenchymal lesions and scars that may cause later problems, such as hypertension, chronic renal failure and, in most cases, end-stage renal disease [10–13]. At the time of diagnosis, 30–49% of children with VUR were reported to have renal parenchymal scarring [14]. UTI, along with other etiologic factors including VUR, is important in the pathogenesis of scarring [15–17]. The risk factors in the development of renal scars include growing kidney, delay in treatment of UTI, recurrence of UTI and higher grade of VUR. The aim of this study was to determine the risk factors for development of renal scarring in patients with primary VUR.

2. MATERIALS AND METHODS

69 children with VUR (42 girls, 27 boys), attending the Pediatric opd were enrolled in the

study. Children included in the study were enrolled into three groups according to their age. Group 1 included children up to 1 year old, group 2 included children aged between one and three years and group 3 included children aged between three and 15 years. Exclusion criteria included urinary tract malformations and clinical signs/symptoms of dysfunctional voiding, such as history of nocturnal and/or diurnal incontinence and urgency incontinence, and elevated voiding frequency associated with recurrent urinary infections and constipation and soiling. Urinalysis, urine culture, renal ultrasonography, voiding cystourethrogram (VCUG) and dimercapto-succinic acid (DMSA) scintigraphy was done. For all children, the VUR investigation was performed after the diagnosis of UTI. Vesicoureteral reflux was graded according to the classification system of the International Reflux Study Committee; grade I indicates reflux into the proximal ureter without dilatation, grade II reflux into the distal ureter without dilatation, and grades III, IV, and V reflux into the distal ureter with mild, moderate, and severe dilatation, respectively [5]. Renal scarring was assessed by DMSA performed minimally six months after the treatment of UTI. Technetium-99m-labeled dimercaptosuccinic acid scans were considered normal if homogeneous uptake of the radioisotope was evident throughout the kidneys and the renal contour was preserved. Renal scarring was defined by the presence of decreased uptake of labeled dimercaptosuccinic acid associated with loss of the contours of the kidney or by the presence of cortical thinning with decreased volume. Renal scarring was classified as type 1: No more than two scarred areas, type 2: Affecting more than two areas, but with remaining normal parenchyma, type 3: Generalized parenchymal damage and type 4: Shrunken end-stage kidney according to the modified scale of Goldraich et al. [7].

2.1 Statistical Methods

Interpretation of results was done using Fischer and chi square tests. SPSS (version 20) and Microsoft excel were used to carry out the statistical analysis of the data.

3. OBSERVATIONS AND RESULTS

Voiding cystourethrography (VCUG) and USG were performed in 69 patients enrolled in the study. Of these 69 patients, 39 had vesicoureteral reflux (56.5%). In terms of renal units, 62.3% units had no vesicoureteral reflux. The individual grades of vesicoureteral reflux (VUR) i.e I, II, III, IV, V in terms of renal units were 11.5%, 28.9%, 40.4%, 19.2% and 0(0%) respectively. The overall VCUG findings are listed in Table 1 and Fig. 1.

Table 1. VCUG findings in patients in terms of renal units

Grades of VUR	No. of renal units
No VUR	63%
VUR I	4%
VUR II	11%
VUR III	15%
VUR IV	7%

VCUG findings were analysed in patients with abnormal ultrasonography. The relationship between abnormal ultrasound and grades of VUR in terms of renal units is depicted in Table 2. Out of the total renal units showing abnormal ultrasonographic findings, (49%) had no VUR while as (6%), (45%) had mild and moderate/severe VUR respectively.

Out of the total 69 patients who underwent VCUG, renal scarring was more likely to occur in

children with documented VUR than those without VUR (17/39 vs 5/30) p value < 0.017.

Among the patients with VUR, scarring was seen to occur more likely in patients with higher grades of VUR (p value < 0.001) (Table 3, Fig. 2).

Table 2. VCUG findings in patients with abnormal USG in terms of renal units

Grades OF VUR	Percentage
No VUR	49
Mild VUR(GR I-II)	6
Moderate/Severe VUR (GR III - IV)	45
Total VUR Units	100

Table 3. Relationship between VUR and renal scarring

Characteristic	No. of patients with scarring	%
No VUR	5	23
VUR	17	77

4. DISCUSSION

VUR, which is common among children with UTI, may result in renal scarring and nephropathy due to reflux of the infected urine to the upper tract. Unless treated promptly, 30–60% of the patients with VUR would have a radiographic evidence of renal scarring [17]. Development of reflux nephropathy and renalscarring is a multifactorial process. Degree of reflux, infection frequency, age at diagnosis, delay in infection treatment and properties of infectious agents are the most important risk factors for renal scarring [18]. Twenty percent and 40% of the children with renal transplantations or on hemodialysis, respectively, have reflux nephropathy [18].

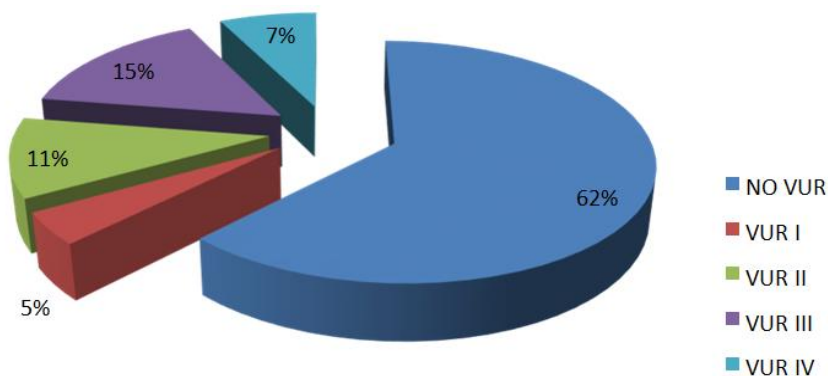


Fig. 1. VCUG findings in patients in terms of renal units

Table 4. Evaluation of other characteristics in children with and without renal scarring

	Scar (+)	Scar (-)	P
Age at diagnosis			
≤1 year	3		>0.05
1–3 years	8	14	
3–15 years	30	14	
Gender			>0.05
Male	12	15	
Female	22	20	
Laterality of VUR			>0.05
Bilateral	12	9	
Unilateral	27	21	
Family history	3	2	>0.05

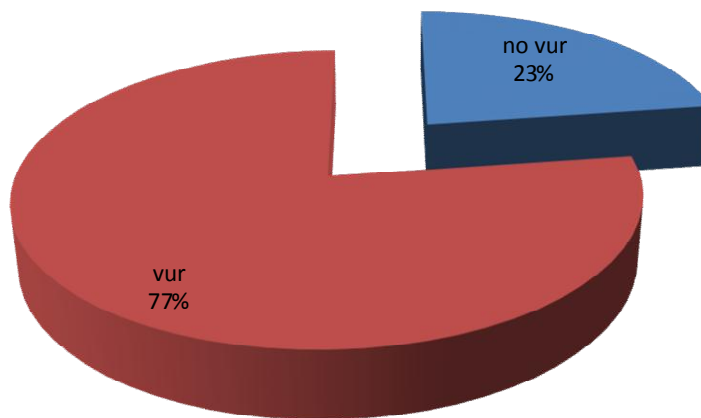


Fig. 2. Graphical representation of relationship between VUR and renal scarring

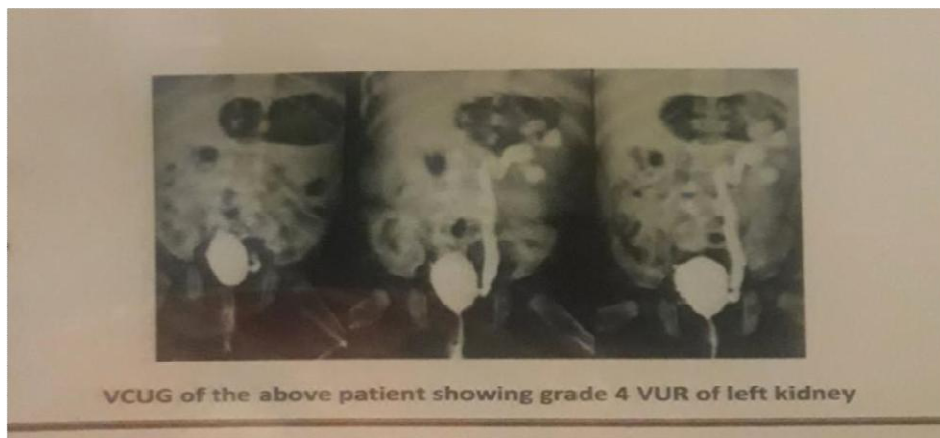


Fig. 3. VCUG showing grade 4 VUR of left kidney

frequency of renal scarring in this study was similar to the values reported previously, which was between 30% and 70% [19,20].

The role of voiding cystourethrography (VCUG) is to identify patients with a vesicoureteral reflux in

presence of acute pyelonephritis or ultrasound abnormalities. In the former case, VCUG may demonstrate a relationship between VUR and renal inflammation and identify high risk group for development of renal scarring (patients with high grade VUR). Renal DMSA scintigraphy used in

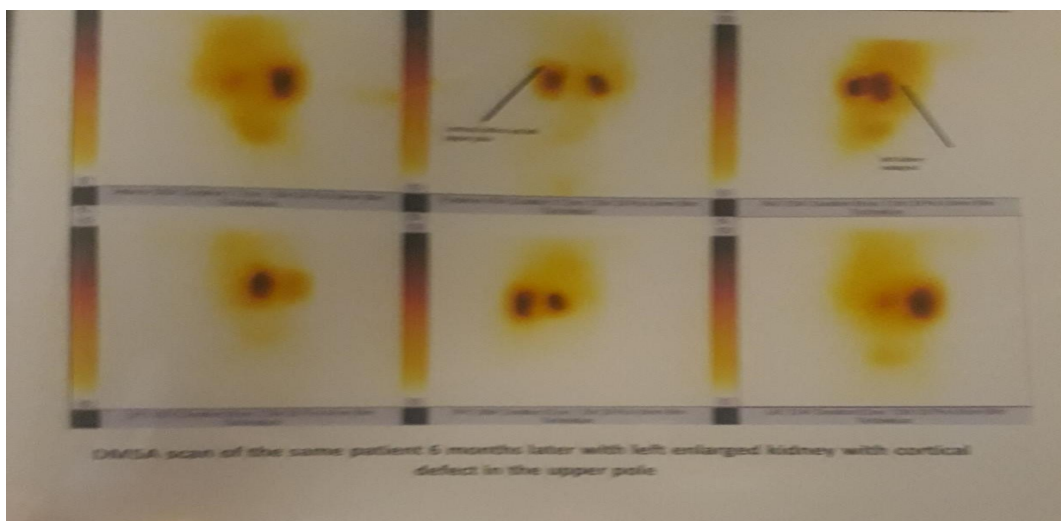


Fig. 4. DMSA scan showing enlarged kidney (left) with critical defect in the upper tract

athis study is considered to be the most sensitive test for the diagnosis of renal scarring. DMSA renal scan because of its superiority over renal ultrasonography for the diagnosis of APN and renal scarring, which has been demonstrated in multiple studies, including experimental studies. Our study revealed a higher risk of preexisting as well as new renal scarring in renal units with grade 4 VUR compared with no VUR or grade 1–3 VUR. These observations support the argument in favor of high-grade VUR being a risk factor for preexisting as well as new renal scarring. However, most children diagnosed with VUR after a UTI have low-grade VUR (grades 1–3), but they remain at some, although lower, risk for renal scarring.

There are controversial results in previous research about the role of gender in the development of renal scarring; some reported no influence and others reported a male predominance [21,22]. In this study, age and gender were not significantly associated with the development of renal scarring. However, there are several studies in which it has been reported that the incidence of renal scarring was higher in children younger than two years when assessed with intravenous pyelography or DMSA. As proposed by previous studies, the severity of the inflammatory process and the volume of kidney involved are the major contributing factors for renal scar formation, independent of age [23]. In other words, both the host immunological defense and the microbiological virulence factors are critical cofactors for renal scarring [24]. UTI is the most common factor that may result in VUR

[25]. There is evidence that infection of the parenchyma is the pre-requisite for formation of renal scars instead of VUR, but scars are more common in children with VUR of grade three or more [26–28]. Familial tendency or trait in etiology of VUR has been reported, but the specific manner of inheritance is still unclear.

5. CONCLUSION

Higher grades of VUR and recurrent UTI were found to be significant risk factors for renal scarring in pediatric patients.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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