

Clinical profile of children with primary vesicoureteric reflux and its association with renal parenchymal scarring

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ABSTRACT

Context: Vesicoureteric reflux (VUR) has been implicated in renal injury before birth as well as in postnatal occurrence of urinary tract infection (UTI) and further renal damage. About 30–49% of children with primary VUR may develop renal scarring called reflux nephropathy. About 5–10% of children with reflux nephropathy may progress to chronic kidney disease in late childhood. **Objectives:** The objectives of the study were to study the clinical profile of children with primary VUR and to assess the relationship with grades of primary VUR and renal parenchymal scarring. **Materials and Methods:** Fifty children of age 1 month–5 years, diagnosed to have Primary VUR, were included in this prospective observational study. Detailed history was taken; examination was carried out as per the study protocol. Investigations included urine analysis, renal function tests, urine culture, renal ultrasonography, micturating cystourethrogram, and ^{99m}Tc dimercaptosuccinic acid (DMSA) scintigraphy. For those who had UTI, DMSA was carried out after a minimum period of 6 months after UTI episode. **Results:** Among the 50 children, 21 (42%) were male and 29 (58%) were female with male-to-female ratio of 0.72:1. Mean age at diagnosis was 9 months, ranging from 1 to 40 months. The number of children presented with UTI was 43 (86%), and 7 children (14%) were asymptomatic and were evaluated in view of abnormality in prenatal ultrasound scan. Unilateral VUR was found in 21 patients (42%), and 29 patients (58%) had bilateral VUR. Of all 79 refluxing units (21 unilateral plus 58 bilateral), 4% had VUR of Grade I severity, 30% of Grade II, 34% of Grade III, 28% of Grade IV, and 4% of Grade V severity. Renal parenchymal scarring on DMSA scan was detected in 42 (54%) of 79 refluxing units including 33% of Grade II, 55% of Grade III, 71% of Grade IV, and 100% of Grade V refluxing units. Prevalence of scarring in complicated, recurrent, and simple UTI was 100%, 93%, and 22%, respectively. **Conclusion:** Risk of renal scarring increased progressively with increasing severity of primary VUR. Complicated and recurrent UTI were found to be statistically significant risk factors for renal scarring. Renal scarring was also seen in absence of UTI in a small percentage of children with primary VUR.

Key words: Primary vesicoureteric reflux, Renal scarring, Urinary tract infection

Vesicoureteric reflux (VUR) is an important predisposing factor for urinary tract infection (UTI) and renal parenchymal scarring [1]. VUR describes retrograde flow of urine from urinary bladder into ureter and kidney. VUR is called primary when it is an isolated finding and referred to as secondary, when associated with other urological anomalies such as posterior urethral valve, renal agenesis, and multicystic dysplastic kidney [1].

Accurate prevalence of VUR is not known as many are asymptomatic and diagnostic testing is performed only when clinically indicated. About 30–40% of children and 40–50% of neonates with UTI have VUR [2]. Of children with primary

VUR, 30–50% may develop renal parenchymal scarring and risk of scarring is reported to be highest in young children [2]. About 5–10% of children with reflux nephropathy may progress to chronic kidney disease (CKD) in late childhood. Reflux nephropathy is also the most common cause of severe hypertension and CKD in childhood and adolescence [2]. The objectives were to study the clinical profile of children with primary VUR and to assess the relationship with grades of primary VUR and renal parenchymal scarring.

MATERIALS AND METHODS

This was a hospital-based prospective observational study conducted over a period of 18 months, from December 2017 to June 2019. Fifty children between 1 month and 5 years of age,

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admitted or attending outpatient department, diagnosed to have primary VUR, were included in the study. Primary VUR was detected in majority of subjects while being investigated after treatment for UTI and in some, diagnosed earlier as a part of workup for prenatally detected congenital anomaly of kidney and urinary tract. Subjects with evidence of secondary VUR such as dysfunctional voiding, neurogenic bladder, urinary tract malformation, and anorectal malformation were excluded from the study.

Detailed history and examination was carried out as per the study protocol. Investigations included urine analysis, urine culture, serum creatinine, renal ultrasonography, micturating cystourethrogram (MCU), and ^{99m}Tc dimercaptosuccinic acid (DMSA) scintigraphy. Blood pressure was recorded at the time of enrolment and during follow-up visits. A midstream clean catch urine or catheterized sample was used for urine examination. Pyuria was considered in presence of >10 leukocytes per mm^3 in a fresh uncentrifuged sample or >5 leukocytes per high-power field in a centrifuged sample [3]. Colony count of >105 CFU/ml was considered to be a significant growth [3].

Subjects with UTI were grouped as simple UTI, complicated UTI, and recurrent UTI [4]. Simple UTI: Low-grade fever, dysuria, frequency, and urgency and absence of symptoms of complicated UTI. Complicated UTI: Presence of fever $>39^\circ\text{C}$, systemic toxicity, persistent vomiting, dehydration, renal angle tenderness, and raised creatinine. Recurrent UTI: Second episode of UTI. UTI was treated with oral and or parenteral antibiotics for 7–10 days and imaging studies (USG abdomen, MCU, and DMSA) following treatment of UTI were carried out as per the guidelines recommended by Indian pediatric nephrology group [4].

VUR on MCU was graded using international reflux grading system. Grade I: Reflux into the non-dilated distal ureter. Grade II: Reflux into the upper collecting system in non-dilated ureter. Grade III: Reflux into dilated ureter but the calyces are not blunted. Grade IV: Reflux into grossly dilated ureter and the calyces are blunted. Grade V: Massive reflux with ureteral dilation and tortuosity and effacement of calyceal details.

^{99m}Tc DMSA scintigraphy was done for all the children recruited in the study to detect renal parenchymal scarring. For those who had UTI, DMSA was carried out after a minimum period of 6 months after UTI episode [5]. Children were followed up at outpatient department during the study period to look for recurrence of UTI and any other relevant problem.

Statistical analysis: Analysis was done using Statistical Package for the Social Sciences (SPSS) version 21. Microsoft Word and Excel were used to generate graphs, tables and results were expressed using appropriate variables.

RESULTS

In this study, out of 50 children, 21 (42%) were male and 29 (58%) were female with male-to-female ratio of 0.72:1 (Table 1). Primary VUR was already diagnosed among 14 children at presentation as a part of workup for prenatally detected dilated collecting system

Table 1: Age and sex distribution at presentation

Age group	Male, n (%)	Female, n (%)	Total, n (%)
1 month–12 months	5 (24)	6 (21)	11 (22)
13 months–5 years	16 (76)	23 (79)	39 (78)

Table 2: Grades of VUR seen on MCU

Grade of VUR	Refluxing units, n (%)	Renal scar, n (%)
I	3 (4)	Zero
II	24 (30)	8 (33)
III	27 (34)	15 (55)
IV	22 (28)	16 (71)
V	3 (4)	3 (100)
Total	79 (100)	42 (54)

VUR: Vesicoureteric reflux, MCU: Micturating cystourethrogram

Table 3: Correlation between clinical profile of primary VUR and prevalence of scarring

Clinical profile of primary VUR	Number of subjects (n=50)	Scar present n (%) 27 (54)	Scar absent, n (%) 23 (46)
Simple UTI	23	5 (22)	18 (78)
Complicated UTI	7	7 (100)	0
Recurrent UTI	13	12 (92)	1(8)
Asymptomatic	7	3 (43)	4 (57)

VUR: Vesicoureteric reflux, UTIU: Urinary tract infection

on USG. Among remaining 36 children, primary VUR was newly detected on being evaluated following UTI. Mean age at diagnosis was 9 months, ranging from 1 to 40 months.

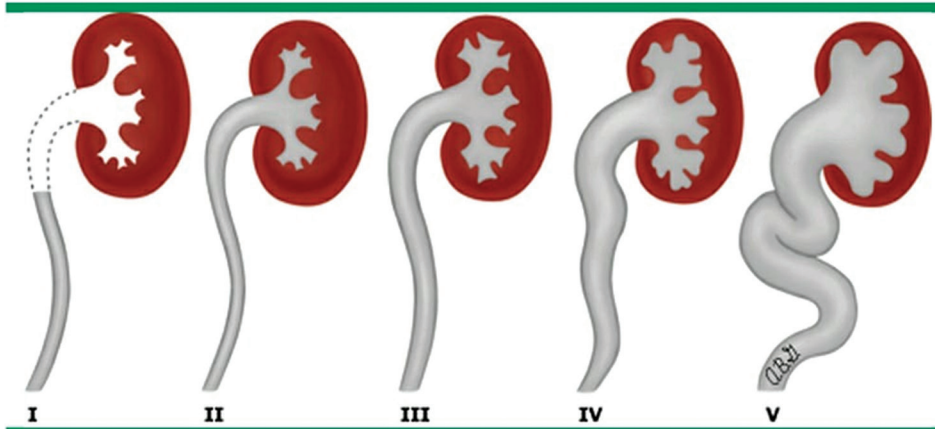
Among 50 children with primary VUR, 43 (86%) children presented with UTI. Of them, 23 (54%) had simple UTI, 13 (30%) had recurrent UTI, and 7 (16%) had complicated UTI. Acute kidney injury was diagnosed in one child with complicated UTI. Seven (14%) of the 50 subjects were asymptomatic and none showed hypertension. Family history of VUR among siblings was found only in three cases. Twenty-one patients (42%) had unilateral VUR, and 29 patients (58%) had bilateral VUR. Of all 79 refluxing units in 50 children (21 unilateral plus 58 bilateral), 4% had VUR of Grade I severity, 30% of Grade II, 34% of Grade III, 28% of Grade IV, and 4% of Grade V severity.

Forty-two refluxing units (54%) in 27 children showed renal parenchymal scarring on DMSA scan. About 33% of Grade II, 55% of Grade III, 71% of Grade IV, and 100% of Grade V refluxing units showed scarring. Thirty-seven refluxing units (46%) in 23 children showed no scarring (Table 2). Of 27 children (54%) who showed renal scarring on DMSA, 24 had suffered from UTI and three were asymptomatic. All children with complicated and recurrent UTI had VUR of Grade III and above, whereas children with simple UTI had Grades I, II, or III (Table 3).

DISCUSSION

Primary VUR results from incompetence of vesicoureteric junction due to shortening and lack of obliquity of the submucosal and intravesical segment of the ureter [1]. The primary concern

International classification of vesicoureteral reflux (VUR)



Modified from: International Reflux Committee. Medical versus surgical treatment of primary vesicoureteral reflux. *Pediatrics* 1981; 67:392.

with VUR is exposing the upper renal tract to infected urine. VUR interferes with effective bladder emptying and results in retrograde flow of urine from ureter into papillary collecting system. In our study of 50 children with primary VUR, UTI was the most common clinical presentation seen in 86% of study population and 7 children (14%) remained totally asymptomatic during the study period.

Our data showed a female preponderance with a male-to-female ratio of 0.72:1 which was similar to RIVUR trial conducted by Carpenter *et al.* [1] and a study by Fidan *et al.* [6] However, most of the studies have shown male preponderance [7]. Mean age of detection of VUR was 9 months overall with 9.5 months in males and 8.6 months in females. Familial tendency was seen only in 6% of cases in our study. There is a huge variability in the reported incidence ranging from 7.7 to 66% [8].

Distribution of grades of reflux in our study was similar to other studies [1], majority belonged to Grades II (30%), III (34%), or IV (28%). Grades I and V were seen in small proportion of cases. Children with complicated (16%) and recurrent UTI (30%) had VUR of Grade III and above, whereas children with simple UTI (54%) had Grades I, II, or III.

UTI along with VUR is classically considered as a risk factor for the development of renal parenchymal scarring. Many studies have established the relation between UTI, VUR, and renal scarring. Degree of reflux, infection frequency, age at diagnosis, delay in infection treatment, properties of infectious agents, and host defense factors are some of the important risk factors for renal scarring [9]. Patients with high-grade reflux (IV and V) are 4–6 times more likely to have renal scarring than those with low-grade reflux (I, II, and III) and 8–10 times more likely than those without VUR [10,11].

In this study, 42 (54%) of 79 refluxing units in 27 children showed renal parenchymal scarring. About 33% of Grade II, 55% of Grade III, 71% of Grade IV, and 100% of Grade V refluxing units showed scarring on DMSA. Risk of scarring increased with increasing severity of primary VUR. Frequency of scarring

in different grades in this study was similar to the observations reported in the previous studies [10,11]. Of 27 children who showed scarring, 24 had suffered from UTI. Highest risk of scarring was seen in children with complicated and recurrent UTI which was statistically significant ($p=0.0002$).

Of seven children without documented UTI, three showed scars on DMSA. Several authors have observed the development of scars in the absence of UTI and questioned the need for antibiotic prophylaxis [11]. This study reiterates that to prevent reflux nephropathy, it is crucial to detect VUR at younger age. Appropriate management minimizes the risk of development of renal scars. For early detection of VUR, imaging studies should be done following treatment of UTI as per the standard guidelines. Imaging studies should also be considered for those with dilated collecting system on prenatal scans and family history of VUR.

CONCLUSION

Risk of renal scarring increased progressively with increasing severity of primary VUR. The highest risk of scarring was seen in children with complicated and recurrent UTI which was statistically significant.

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