Clinical Course and Effective Factors of Primary Vesicoureteral Reflux

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Abstract- Vesicoureteral reflux (VUR) is one of the most important causes of urinary tract infection and renal failure in children. It is a potentially self-limited disease. The aim of this study was to evaluate the clinical course and significant factors in children with primary VUR. The medical charts of 125 infants and children (27.2 % males, 72.8% females) with all grades of primary VUR were retrospectively reviewed. Mean age at diagnosis was 22.3±22.9 months. 52% of patients had bilateral VUR. Mild reflux (Grade I, II) was the most common initial grade. 53.6% of patients achieved spontaneous resolution. 30.1% of patients had decreased renal function on initial DMSA renal scan, significantly in males and severe VUR. Reflux nephropathy occurred in 17.6% of patients, especially in renal damage and male sex. No significant association was observed between recurrent urinary tract infection with the severity of VUR, and the presence of renal damage at admission. Age at diagnosis, gender, grade, laterality, the absence of recurrent urinary tract infection and renal damage had a significant correlation between spontaneous VUR resolution. Spontaneous resolution of primary VUR occurred significantly in female patients, age ≤ 30months at diagnosis, mild-to-moderate VUR, unilateral reflux, the absence of recurrent urinary tract infection, and renal damage.

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Introduction

Vesicoureteral reflux (VUR) is one of the most important risk factors for urinary tract infection (UTI), presents in 29-50% of children with UTI and 10% of patients with prenatal hydronephrosis (1). The ability of spontaneous VUR resolution influences the appropriate follow-up schedules, patient counseling, treatment strategy, and antibiotic prophylaxis (2).

Different significant variables have been reported in the clinical course of VUR in children. Conservative treatment has been suggested in asymptomatic infants < one year, irrespective to VUR grade and asymptomatic children older than one year with mild-moderate VUR (3). Previous renal damage has been considered a predictor of VUR worsening, and surgical treatment has been recommended for severe VUR with renal damage (4). In addition, recurrent UTI, bladder dysfunction, abnormal renal ultrasound, and decreased renal function have been reported as risk factors of non-resolution (5,6). But, male gender, infants less than one-year-old, single ureter, low-grade VUR, unilateral VUR and gradual improvement of VUR has been suggested the predictors of spontaneous resolution (7,8). A few studies have been performed to evaluate the clinical course of VUR in Iranian children. This study aimed to evaluate the clinical course and significant factors in children with primary VUR.

Materials and Methods

A total of 125 patients with primary VUR admitted to Aliasghar Children's Hospital or visited in the office of two nephrologists from 2002-2012 were enrolled in this retrospective study. Patients with secondary VUR including posterior urethral valve, ureterocele, ectopic ureter, megaureter, duplicated ureter, bladder exstrophy, neurogenic bladder, structural bladder abnormalities, and Hinman's syndrome were not included in this study. Also, patients older than 18 years, those with incomplete

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follow-up and persistent VUR were excluded.

The diagnosis was made by voiding cystourethrogram in the majority of patients. Direct radionuclide cystography was especially performed in girls with a negative history of neurogenic bladder, highly suspicious VUR with negative voiding cystourethrogram, and for follow-up studies. Reflux was graded based on the results of the voiding cystourethrogram in five grades (grade I-V) according to the International Reflux Study in Children. Based on direct radionuclide results, VUR was graded as mild (corresponding to grades I, II), moderate (corresponding to grade III), and severe (corresponding to grades IV, V).

In patients with bilateral reflux of different grades, the higher grade was used for statistical analysis. Demographic and clinical characteristics including age at diagnosis, age at resolution, sex, blood pressure, history of recurrent UTI, initial grade, laterality (unilateral, bilateral), and findings on DMSA renal scan were compared between patients with spontaneous resolution and those who underwent surgical treatment. UTI was defined as the growth of at least 105 colony forming units/ml urine in mid-stream sample or urine bag in symptomatic patients or any growth in suprapubic aspiration.

Recurrent UTI was applied to two or more episodes of UTI occurring during a six months period. Reflux nephropathy defined as renal damage secondary to VUR, presented as hypertension, decreased renal function or shrunken kidney on DMSA renal scan. Hypertension was considered as blood pressure more than 95% for height, age, and sex.

Patients were followed up with quarterly urine cultures and repeated cystograms at 18-24 months periods or more. Spontaneous VUR resolution was defined as at least one cystogram becoming normal. A case of bilateral reflux was not considered resolved until each ureter demonstrated reflux resolution. Surgery was performed in children with high-grade VUR for age at diagnosis or during follow-up, old age at first diagnosis according to VUR grade, breakthrough infections, and reflux nephropathy.

The Fisher exact test and chi-square test were used to compare categorical variables. Two-sample t and Wilcox rank sum tests were used to compare continuous and ordinal variables. Odds ratio (OR) and 95% confidence intervals (95% CIs) were used for group risk comparison. Data were analyzed by SPSS® version 19. *P*-value<0.05 was considered to be statistically significant.

Results

Mean age at the time of diagnosis was 22.3 ± 22.9 months. Median age at diagnosis for boys and girls was 18 (range 0.5 to 60) and 12 months (range 1 to 84), respectively. Of the patients, 72.8% were girls. Bilateral reflux was documented in 65 patients (52.0%). Mild VUR was the most common initial grade (44%), followed by moderate (32.8%) and severe reflux (23.2%).

A total of 31 (30.1%) patients (62.5% boys, 20.3% girls) had decreased cortical uptake on initial DMS scan. There was a strong association between male sex and severity of VUR with renal damage. Totally, 25% of patients with mild or moderate VUR and 47.8% with severe VUR had cortical damage at presentation. This difference was statistically significant (*P*= 0.03).

Corrective surgery was performed in high-grade VUR for a specific age (72.4%), old age at presentation (10.4%), and reflux nephropathy (15.5%). One patient (1.7%) underwent surgery for both advanced grade and reflux nephropathy. Open anti-reflux surgery was the most common surgical procedure.

Of the patients, 67 (53.6%) achieved spontaneous resolution and 58 (46.4%) underwent surgical intervention. Mean age at surgery was 61.2 months and 39.7 months in patients with spontaneous resolution. Mean time from diagnosis to surgical correction was 34.8 ± 33.7 months vs. 23.2 ± 11.0 until spontaneous resolution.

Female gender (OR=4.02, 95% CI 1.72–9.43, *P*=0.001), age ≤ 30 months at diagnosis (OR=2.62, 95% CI 1.06–6.51, P=0.04), mild-to-moderate VUR (OR=5.24, 95% CI 2.03–13.48, P=0.001), negative history of recurrent UTI (OR=4.34, 95% CI 1.71–11.02, *P*=0.002), lack of renal damage at the time of diagnosis (OR=5.48, 95% CI 2.19–13.60, *P*<0.001), and unilateral reflux (OR=2.81, 95% CI 1.36–5.84, *P*=0.005) were significantly associated with spontaneous reflux resolution. Table 1 Summarizes the demographic and clinical characteristics compared between patients in whom VUR resolved and those in whom surgery was carried out as well as the statistical differences between them.

Significant association was not observed between recurrent urinary tract infection with severe grade of VUR (OR=2.57, 95% CI 0.52–8.08, *P*=0.11), and the presence of renal damage at diagnosis (OR=1.01, 95% CI 0.40–2.54, *P*=0.99). Seventeen patients (13.6%) presented with increased serum creatinine. Seven of them had bilateral VUR. The statistically significant association was not observed between abnormal serum creatinine level and bilateral reflux (OR=0.60, 95% CI 0.21–1.70, *P*=0.34).

Reflux nephropathy occurred in 22 (17.6%) patients, especially in the male gender of which, 17 had abnormal serum creatinine level. Reflux nephropathy was strongly associated with renal scar at the time of diagnosis (P<0.001), and male gender (P=0.01). Similarly, hypertension was strongly associated with renal scars (OR=14.1, 95% CI 1.70-116.62, P<0.01), and abnormal serum creatinine level (OR=19.1, 95% CI 4.18-87.18, P<0.001).

Table 1. Demographic and clinical characteristics of children with and without spontaneous reflux resolution

Characteristic		Outcome		*P*-value
		Surgery	Spontaneous resolution	
No of patients		58 (46.4%)	67 (53.6%)	
Age at diagnosis	**Mean ± SD**	25.1±21.4	16.0±14.6	0.001
	Median	18	10	
	Range	1-84	0.5-66	
Sex	**Female**	34 (58.6%)	57 (85.1%)	0.001
	Male	24 (41.4%)	10 (14.3 %)	
Grade	**Mild**	10 (17.2%)	45(67.2%)	<0.001
	Moderate	26 (44.8%)	15(22.4%)	
	Severe	22 (37.9%)	7(10.4%)	
Bilateral reflux		38 (65.5%)	27 (40.3%)	0.007
Renal damage		21(51.2%)	10 (16.1%)	<0.001
Recurrent UTI		56 (96.6%)	45 (67.2%)	<0.001

Discussion

In this retrospective study, we report the clinical course of a group of children with primary VUR. Most of the patients were managed medically. At baseline, a predominance of girls was observed, a finding similar to previous reports (9). Mean age at diagnosis was slightly younger than previous reports (10).

At admission, 30.1% of patients already presented with decreased renal uptake on DMSA renal scan, which was significantly higher in children with severe reflux. Smellie *et al.,* also reported the association of VUR grade with the presence of the renal scar. In their series, the renal scar was seen in 69% of children with moderate/severe VUR and 24% of those with mild reflux (11). Goldraich *et al.,* reported a higher incidence of renal scar in high-grade reflux than mild VUR (10). Wang *et al.,* in a clinical analysis of 135 children with primary VUR found a higher incidence of renal scar in moderate and severe VUR than mild reflux (12). Abeysekara *et al.,* indicated a higher incidence of renal scar in severe (grades IV-V) compared to mild reflux (13).

In the present study, a strong association was found between male gender and renal damage on DMSA renal scan. Previous studies have shown a predominance of renal scars in boys with primary VUR, which is probably congenital (14).

In this study, recurrent UTI was not associated with grade of VUR, or presence of renal scars at admission. In the study by Smellie *et al.,* on 226 patients, no association was reported between recurrent UTI with the severity of VUR or renal scarring (11). Goldraich *et al.,* have also shown a greater incidence of breakthrough UTI in girls, irrespective of VUR grade (10). Silva *et al*., found an association between recurrent UTI and female gender, dysfunctional voiding and constipation (1).

Spontaneous resolution occurred in 53.6% of patients in the current study. Reflux resolved spontaneously in 68% of patients in Schwab study (15). Smellie *et al.,* reported VUR improvement in 52% of patients during 10 years follow-up. Significant resolution occurred in VUR grade III versus IV, unilateral VUR, and age ≥ 5 years at diagnosis (16). Silva *et al.,* in a cohort of 506 medically managed children with VUR identified race, low-grade VUR, the absence of renal damage and voiding dysfunction as independent predictors of reflux resolution (17). Male sex, age younger than one year of diagnosis, low grade at presentation, unilateral reflux, and improvement from the previous year at any point, bladder volume more than 50% of predicted capacity at reflux onset, history of prenatal hydronephrosis and negative history of breakthrough UTI were significant variables of VUR resolution in other studies (18-20). In this study, age ≤ 30 months, female sex, mild-to-moderate reflux, the

absence of recurrent UTI, lack of renal damage at the time of diagnosis, and unilateral reflux were associated with spontaneous reflux resolution. However, these strong associations might be partly explained by the exclusion of patients who were still being followed by the report.

In our series, 17 children (13.6%) had abnormal serum creatinine levels at the time of initial diagnosis. Smellie *et al*., showed a prevalence of 2.2% (5/226) of elevated plasma creatinine levels in 226 patients (11).

Hypertension was documented in 7.2% of our patients at diagnosis. Hypertension occurred in 3% of 735 patients with VUR in Silva *et al.,* study (1). Zhang and Bailey reported a long-term follow-up of adults with reflux nephropathy (mean age at presentation: 17.3 years) and reported that 8.5% (25/294) and 4.8% (14/294) of patients had hypertension and proteinuria at presentation, respectively (21).

In conclusion, Spontaneous resolution of primary VUR occurred significantly in female patients, age ≤ 30 months at diagnosis, mild-to-moderate VUR, unilateral reflux, and absence of recurrent UTI in this study. It is suggested to consider medical follow-up in females, young, low grade, and unilateral VUR without a history of recurrent UTI instead of surgical treatments.

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