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Clinical Course of 250 Pediatric Cases of Vesicoureteral Reflux in Zahedan, Southeast of Iran

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Introduction: Although the incidence of primary reflux is 0.1-1.3% in the general population, it is much higher (29-50%) in children with urinary tract infection (UTI). This study aimed to evaluate the epidemiologic characteristics and outcome of vesicoureteral reflux (VUR) in Iranian children in Zahedan, southeast of Iran.

Materials and Methods: In this historical cohort study, we reviewed all records of 250 patients diagnosed with VUR who were referred to a Pediatric Nephrology Clinic in Zahedan, Iran between April 2008 and September 2009 and were followed until June 2011. The diagnosis of VUR was made by convectional voiding cystourethography (VCUG). Following the diagnosis, patients received prophylactic low-dose oral antibiotic and were followed by radionuclide cystography (RNC) for 18 months.

Results: Of 250 patients with VUR, 153 (61.2%) were female with a mean age of 2.7 ±2.0 years at presentation. One hundred and thirty patients (52%) had unilateral VUR and 120 patients (48%) had bilateral VUR. In 54.4% of the patients, VUR was detected during the investigation for UTI and 13.2% had prenatal hydronephrosis. Voiding dysfunction was the most important condition with VUR (15.2%). Kidney ultrasound confirmed abnormal results in 73.2% of the patients. Renal scarring secondary to VUR was detected in 85 (34%) patients at the time of VUR diagnosis.

Conclusions: Our data showed that VUR was significantly higher in female children and the frequency of abnormal renal scan was significantly higher in children with high-grade VUR. Further studies may be needed to determine the risk factors and apply effective interventions to minimize the progression of renal damage.

Keywords: Vesicoureteral reflux; Child; Zahedan.

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Introduction

Vesicoureteral reflux is the retrograde flow of the urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder is normally oblique, between the bladder mucosa and the detrusor muscle, creating a flap-valve mechanism which prevents reflux.

Reflux occurs when the submucosal tunnel between the mucosa and detrusor muscle is short

or absent [1]. Although the incidence of primary reflux is 0.1-1.3% in the general population, it is much higher (29-50%) in children with urinary tract infection (UTI), predominantly in females (80%) with a mean age of 2-3 years at diagnosis [2]. Primary reflux (10%) may also be detected during evaluation for prenatal hydronephrosis [2-3]. Reflux predisposes the patient to pyelonephritis by facilitating the transport of

bacteria from the bladder to the upper urinary tract. The inflammatory reaction caused by a pyelonephritic infection can result in renal injury or scarring, also termed reflux-related renal injury or reflux nephropathy [1]. Voiding cystogram (VCUG) is the main diagnostic modality for detecting vesicoureteral reflux (VUR) [4]. A VUR grading system including five grades has been suggested by the International Reflux Study (IRS). The goal of treatment is to prevent pyelonephritis, reflux related renal injury, and other complications of reflux [4]. In 1997, the American Urological Association (AUA) published a treatment guideline for VUR. Medical therapy is based on the principle that reflux is often resolved over time so that morbidity or complications of reflux may be treated without surgery by preventing UTI. Surgical therapy is advised for children with ongoing reflux leading to renal injury or other reflux-related complications so that the likelihood of these problems is minimized by eliminating reflux [5]. The current study aimed to evaluate the clinical feature, renal damage, and prognosis of vesicoureteral reflux (VUR) in children.

Materials and Methods

In this retrospective analysis, we reviewed all records of 250 patients diagnosed with VUR who were referred to the Pediatric Nephrology Clinic of Ali-Asghar Hospital, Zahedan, Iran between April 2008 and September 2009 and were followed until June 2011. This hospital is a referral hospital in Sistan & Baluchistan Province and all patients are visited by the only pediatric nephrologist in the province. Children with asymptomatic bacteriuria, urinary tract obstruction, urogenital malformation, neurogenic bladder, and severe neurological or systemic disease were excluded from the study.

The data included age at diagnosis, clinical features, unilateral or bilateral reflux, VUR grade, renal damage, renal function, dysfunctional voiding and other anatomic abnormalities. The diagnosis of VUR was made by convectional voiding cystourethography (VCUG). The grade of reflux was classified according to the system proposed by the International Reflux Study Committee. Voiding dysfunction was defined as the presence of daytime incontinence, urgency, and frequency supported by sonography findings. Renal damage was evaluated by Technetium 99m (Tc-DMSA) scan. DMSA scan was carried out after at least 3 months from UTI clearing in infants and

children. Renal damage was determined qualitatively by imaging findings and the patients were classified as normal and abnormal.

Abnormal ultrasonography was defined as hydronephrosis, ureter dilation, cortical echogenicity, increased kidney size, and decreased cortical thickness.

After diagnosis, the patients were followed according to a systematic protocol for two years at 1-1.5 year intervals [6]. All children received antibiotic prophylaxis and urine cultures were obtained. Follow up imaging included direct isotope cystography and DMSA scan. The criterion for reflux resolution was negative findings on direct isotope cystogram. Recurrent UTI was defined as growth of 100,000 cfu/ml in the bag-collected or midstream urine together with urinary symptoms.

The study was approved by Ethics Committee of Zahedan University of Medical Sciences (registration number=1207). Data were analyzed using chi-square and logistic regression in SPSS 15.

Results

Of 250 patients with VUR, 153 (61.2%) were female with a mean age of 2.7 ± 2 years at presentation, ranging from 8 months to 13 years. One hundred and thirty patients (52%) had unilateral VUR and 120 patients (48%) had bilateral VUR. In 54.4% of the patients, VUR was detected during investigation for UTI and 13.2% had prenatal hydronephrosis. Voiding dysfunction was the most important condition with VUR (15.2%). Kidney ultrasound confirmed abnormal results in 73.2% of the patients. Renal scarring secondary to VUR, which is called reflux nephropathy, was detected in 82 (34%) patients at the time of VUR diagnosis (Table 1).

According to Table 2, left and right ureters were almost equally affected by VUR (75.2% vs. 72.8%). Of all refluxing ureters, the most frequent grade was III (n=110; 44%) and the frequency of grades I and V was similar (n=24; 9.6%) (Table 1). For re-evaluation of the VUR status, VCUG was repeated in 88 patients after 18 months and VUR was detected in 74 renal units. However, 30.77% of the patients showed spontaneous complete resolution, 17.95% had improvement in VUR grading, 16.24% showed no change or deterioration, and 35% were referred for surgery. VUR grading was not significantly different between sex (P=0.96) and age groups (0.92).

Table 1. Clinical and imaging findings in children with vesicoureteral reflux

Patients characteristics		N (%)
Clinical symptom	Urinary tract infection	136(54.4)
	Enuresis	36(14.4)
	Prenatal hydronephrosis	33(13.2)
	Urinary tract anomaly	23(9.2)
	Stone	14(5.6)
	Other *	8(3.2)
	Sonography	Abnormal
VCUG	Unilateral	130(52.0)
	Bilateral	120(48.0)
VCUG Grading	Grade I	24(9.6)
	Grade II	52(20.8)
	Grade III	110(44.0)
	Grade IV	40(16.0)
	Grade V	24(9.6)
DMSA	Abnormal	82(34.0)

Univariate analysis showed no significant relationship between renal scar and gender (P=0.99) and laterality of VUR (P=0.55). However, the odds of renal scarring increased significantly by age (P=0.001). Children with UTI relapse had a higher chance of renal scarring than others (P=0.03). Renal scarring increased from 2 (8.3%) in patients with grade I to 18 (75%) in patients with grade V. According to multivariate analysis, only VCUG grading and age had a significant relationship with renal scarring. The odds of renal scarring in patients with grade V were 39.5 times higher than those with grade I. Furthermore, patients over 5 years old experienced renal scarring 3 times more than those under one year of age (Table2, 3).

Table 2. Distribution of initial VUR grading in refluxing renal units

VUR grading	Left	Right
I	14(5.6)	22(8.8)
II	39(15.6)	55(22)
III	78(31.2)	76(30.4)
IV	38(15.2)	16(6.4)
V	19(7.6)	13(5.2)
Total	180(75.2)	182(72.8)
No VUR involvement	62 (24.8)	68 (27.2)

Discussion

Vesicoureteric reflux (VUR) is a common abnormality affecting about one third of children presented with urinary tract infection (UTI) at young age. Diagnosis and effective management of patients with renal damage due to UTI is vital,

especially when it is accompanied by VUR resulting in hypertension and renal failure. This study aimed to evaluate the epidemiologic characteristics and outcome of VUR in children in Zahedan, southeast of Iran.

In the current study, 153 girls (61.2%) and 97 boys (38.8%) with VUR were evaluated. A male predominance (65%) was reported in Chinese (65%) and Korean (61.9%) children [4-6]. The dominance of females may be due to higher incidence of UTI in females than males in our study population. In the current study, there was no significant relationship between renal scar and gender (P=0.99), which is in line with the results of several studies [5,11,12]. Furthermore, similar to other studies, age and VCUG grading were significantly associated with renal scarring [5,12].

In the current study, the odds of renal scarring in patient with grade V was 39.5 times higher than those with grade I. Similar results have been reported in the literature. Association between all subtypes of renal damage with high grade reflux (III-V) and abnormal renal scan is more frequent in patients with high grade reflux, especially in patients under one-year-old [5]. Furthermore, renal scar was found twice as often in VUR patients with grade IV-V compared to grade I-III [3,12]. Therefore, VUR severity can be considered a significant risk factor for renal scarring and possible formation of renal scars that may result in end stage renal failure.

In this study, kidney ultrasonography was abnormal in 73.2% of the patients. In one study, the sensitivity and specificity of ultrasonography for diagnosis of VUR was reported 63% and 91%, respectively [10]. Another study reported a sensitivity, specificity, PPV, and NPV of 30%, 84%, 46%, and 72% for ultrasonography in prediction of VUR, respectively. Therefore, using ultrasonography for prediction of VUR is not recommended and VCUG is preferred instead [9]. In this study, the majority of the patients (54.4%) presented with UTI. Studies in other populations have shown a higher frequency of UTI (90% - 93%) [4,6]. Additionally, 95% of the patients with VUR are found while looking for UTI [2]. Early diagnosis of VUR in children with first UTI helps to prevent recurrences by using prophylactic antibiotic therapy [1].

Some studies have shown that voiding dysfunction and constipation are associated with UTI recurrence [1,5]. In the current study, voiding dysfunction (15.2%) was the most important condition detected in patients with VUR. Therefore, we believe that patient with VUR

Table 3. Dimercaptosuccinic acid (DMSA) findings

DMSA		Abnormal (n%)	P-value	OR (95% CI)	Adjusted* OR (95% CI)
Gender	Male	33(34.0)	0.99	1.01 (0.59, 1.71)	---
	Female	52(34.0)		1.00	
VCUG Grading	I	2(8.3)	0.001	1.00	1.00
	II	7(13.5)		1.71 (0.33, 8.93)	1.88 (0.35, 9.97)
	III	32(29.1)		4.51 (1.01, 20.32)	4.89 (1.07, 22.38)
	IV	26(65.0)		20.43 (4.18, 99.83)	22.77 (4.54, 114.14)
	V	18(75.0)		33.00 (5.93, 183.79)	39.52(6.87,227.21)
Age (year)	≤1	32(26.4)	0.01	1.0	1.00
	1-5	33(38.4)		1.73 (0.96, 3.14)	1.83 (0.93, 3.6)
	>5	20(46.5)		2.42 (1.17, 5.00)	3.01 (1.32, 6.88)
VCUG	Unilateral	42(32.3)	0.55	1.00	---
	Bilateral	43(35.8)		1.17 (0.69,1.98)	
UTI Relapse	Yes	41(41.8)	0.03	1.75 (1.03, 3.00)	---
	No	44 (29.1)		1.00	

* Only significant factors in multivariate model have been revealed.

should be carefully evaluated for voiding dysfunction and constipation. Although VCUG was not recurrent in some low risk patients, the overall spontaneous complete resolution or improvement of our patients was 48.7% after 18 months. A study in Shiraz, Iran in 2007 showed a spontaneous resolution rate of 55% for VUR in a 4.5-year follow-up [2]. Other studies have reported a spontaneous resolution rate of 39%-80% [2,6,8]. These results are compatible with the worldwide trend of medical management of primary VUR and avoidance of invasive surgical methods. In the current study, lower grades of VUR had a higher rate of spontaneous resolution, which was in line with the results of another study indicating significant differences in the resolution based on VUR grading [13]. This study emphasizes the benefits of medical therapy and careful follow up as reported in other studies [2,8]. It is recommended that VUR grade I to IV may be managed medically with low dose oral antibiotic prophylaxis. Surgery should be reserved for breakthrough, high grade, persistent UTI that causes renal scar formation. Further studies may be required to determine risk factors and effective interventions to minimize the progression of renal damage.

Conclusions

We reviewed all records of 250 patients diagnosed with VUR who were referred to the Pediatric Nephrology Clinic of Ali-Asghar Hospital, Zahedan, Iran between April 2008 and September 2009 and were followed until June 2011. Our data showed that VUR was significantly higher in female

children and the frequency of abnormal renal scan was significantly higher in children with high-grade VUR. Further studies may be needed to determine the risk factors and apply effective interventions to minimize the progression of renal damage

Conflict of Interest

None declared

Financial Support

None declared

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