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A 5-year retrospective analysis of patients with primary vesicoureteral reflux undergoing open surgery; an assessment of 60 patients

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Abstract
Vesicoureteral reflux (VUR) describes the backward flow of urine from the bladder to the ureter and/or kidney. In this study, 60 patients below 18 years of age diagnosed with primary VUR in our clinic between 2010 and 2014 and undergoing ureteroneocystotomy using various open surgery techniques were evaluated retrospectively. Diagnosis of VUR was based on voiding cystourethrography (VCUG). Urinary system ultrasonography (USG) was performed to exclude possible additional pathologies and to monitor the clinical course. Static renal scintigraphy (DMSA) was performed to determine preoperative renal scars and loss of function. Severity of reflux was divided into 5 degrees (1-5) following the criteria set out by the International Reflux Study Group. Patients were divided into 3 groups, mild (grade 1-2), moderate (grade 3) or severe (4-5) VUR. Females constituted 71.7% of the patients (n=43). Mean age at time of diagnosis of VUR was 6.25 years and mean age at time of surgery was 6.36 years. Fifteen percent of VURs were on the right side (n=9), 31.7% were on the left side (n=19) and 53.3% were bilateral (n=32). Advanced grade VUR (grade 4-5) was determined in 68.3% of patients. Loss of function was observed in 27.7% (n=16) of patients undergoing DMSA, and scar and loss of function were determined in 46.7% (n=28). The most common pathogen grown in preoperative urine cultures was Escherichia coli (65%). No significant difference was observed between the VUR grades in terms of age at time of diagnosis or age at time of surgery (p=0.682 and p=0.673, respectively). No statistically significant correlation was also determined between gender and VUR grade (p=0.859). No patient required a second surgical procedure. At postoperative follow-up, hypertension was observed in two patients, and these received antihypertensive therapy. Hypertension was observed over the long-term in one patient and was controlled with antihypertensive therapy. In conclusion, a high level of loss of renal function and scars was determined, in parallel with greater age at time of diagnosis of VUR and at time of surgery, in our region.

Keywords: Vesicoureteral reflux, child, open surgery

Introduction

Vesicoureteral reflux (VUR) describes the backward flow of urine from the bladder toward the ureters and/or the kidney. VUR may develop primarily, in association with congenital uretrovesical anomaly, or secondarily due to anatomical or functional causes [1,2]. The prevalence of VUR in the normal population is approximately 1% [3-5]. This varies between 30% and 50% in children diagnosed with recurrent urinary tract infection (UTI) [6]. Although the prevalence is higher in females, boys with intrauterine hydronephrosis are more affected [7].

Many patients with VUR are identified by means of hydronephrosis determined at ultrasonography (USG) in the intrauterine period or during urinary infection. The condition may rarely appear with uremic symptoms associated with advanced reflux nephropathy or with findings of coronary insufficiency secondary to untreated hypertension [7]. VUR lays the foundation for acute urinary infection and is one of the most common causes of nephropathy in children. Increased scarring in the kidney may gradually lead to hypertension, proteinuria, loss of renal functions and sometimes end stage kidney failure [8-10].The primary objective in the treatment of VUR is therefore to obviate potential renal scarring and losses of renal function by preventing urinary system infections and associated pyelonephritis attacks. Although the preferred option in mild (grade 1-3) and asymptomatic cases is a conservative approach with antibiotic prophylaxis, endoscopic intervention or open surgery must be considered in order to prevent potential renal scarring and loss of function in these cases when recurrent infection attacks cannot be prevented and in more severe (grade 4-5) cases [9,11].

Although open surgery is a more invasive procedure than endoscopy, due to its low complication and high success rates it may be preferred in all cases of VUR, particularly in severe cases, in which renal scarring and function loss are determined [12]. The purpose of this study was to perform a retrospective examination of patients undergoing open surgery due to primary VUR over a 5-year period.

Method

Sixty patients aged under 18 diagnosed with primary VUR and undergoing ureteroneocystotomy via open

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surgery between 2010 and 2014 were evaluated retrospectively. Open surgery was performed after 6 months in cases that did not resolve following subureteric injection and that continued to experience UTI. Patients whose reflux resolved entirely following subureteric injection or without UTI and with significant improvement in reflux and cases of secondary VUR associated with anatomical or functional causes were excluded from the study. VUR was diagnosed on the basis of voiding cystourethrography (VCUG) performed in cases receiving treatment for recurrent UTI and 3 weeks after end of treatment. Two or more UTIs in the previous 6 months were regarded as recurrent infection. Reflux was classified according to five degrees of severity (1-5) set out by the International Reflux Study Group[13].Patients were classified as mild (grade 1-2), moderate (grade 3) or severe (grade 4-5). Urinary system USG was performed in order to exclude possible additional pathologies and to monitor clinical course in all cases. Preoperative renal scarring and function loss were determined using DMSA. However, DMSA data were only available for 49 patients (81.7%), records for 11 patients being unavailable since scintigraphy was performed in external centers. Proteinuria, hypertension, blood urea and creatinine values were determined for all patients. Hypertension was defined as systolic or diastolic blood pressure values above the 95th percentile value for age, sex and height. Surgical techniques (Cohen, Lich-Gregoir, Politano LeadBetter) were determined depending on whether reflux was unilateral or bilateral and on location of the ureteral orifice. Urinalysis and urinary USG tests were performed in the 1st month postoperatively and subsequently at 6-month intervals. Cases with an entirely problem-free course were monitored using USG alone, while 33 (55%) patients with postoperative urinary system symptoms or in whom monitoring was difficult for social reasons underwent VSUG at the 6th month postoperatively.

Statistical analysis: Descriptive data were expressed as mean plus standard deviation, and categoric data as numbers and percentages. The chi-square test, Fisher's Exact test, the Kruskal Wallis test and One-Way Analysis of Variance were performed as hypothesis tests. Analyses were performed on SPSS software, and significance was set at <0.05.

Results

Sixty patients were included in the study, 28.3% (n=17) male and 71.7% (n=43) female.VUR was located on the right side in 15% (n=9) of patients, on the left in 31.7% (n=19) and was bilateral in 53.3% (n=32). Numbers and percentages by degrees of VUR are shown in Table 1.

Table 1. Numbers and percentages of patients' VUR degrees

VUR degree	Number	%
Grade 1	3	5.0
Grade 2	5	8.3
Grade 3	11	18.3
Grade 4	23	38.3
Grade 5	18	30.0
Total	60	100

Age during surgery, age at diagnosis of VUR, preoperative creatinine and blood urea nitrogen (BUN) values, preoperative UTI numbers, total UTI in the previous year and febrile UTI numbers were examined for all patients. Minimum, maximum, mean and standard deviation values for these parameters are shown in Table 2.

Table 2. Patients' clinical and laboratory characteristics

	No.	Minimum	Maximum	Mean	Std. Deviation
Age at diagnosis of VUR (years)	60	0	14	6.25	2.98
Patient's age at time of surgery (months)	60	12	168	76.33	35.70
*Preoperative blood creatinine value	59	0.16	2.90	0.51	0.37
$^{+}$Preoperative BUN value	56	7	107	30.07	16.15
Number of preoperative UTIs	32	0	15	4.88	3.63
Number of preoperative febrile UTIs	32	0	15	3.94	3.60
Total number of UTIs in the previous 1 year postoperatively	53	0	12	0.70	2.13
Number of febrile UTIs in the previous 1 year postoperatively	53	0	7	0,25	1,07

*, normal range; 0.72-1,=.25 mg/dL; $^{+}$, BUN: blood urea nitrogen, normal range; 8.4-25.2 mg/dL

The most commonly grown pathogen in preoperative urine cultures was *Escherichia coli* (65%).

Preoperative urinary dysfunction was present in 38.3% (n=23) of patients. Distribution of types of urinary dysfunction is shown in Figure 1.

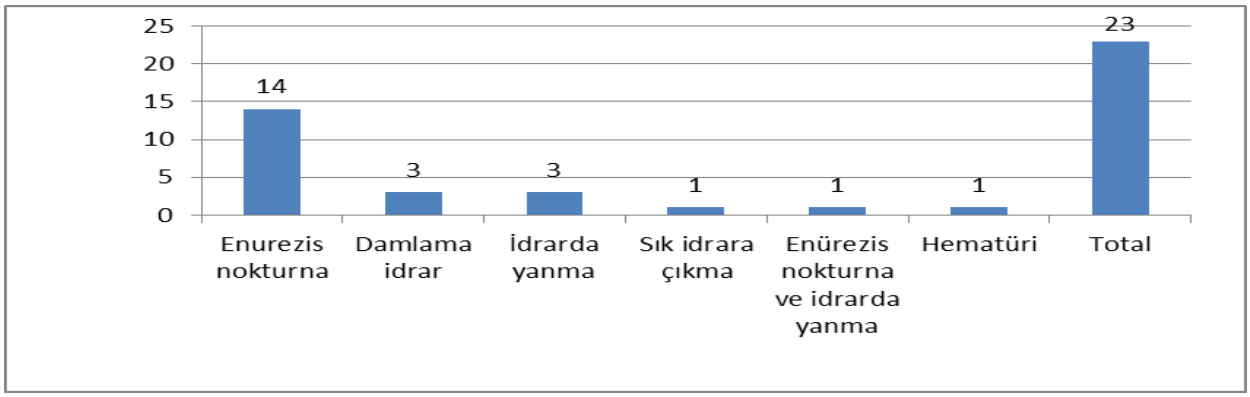

Figure1. Distribution of types of preoperative urinary dysfunction

In terms of patients' preoperative DMSA data, 8.3% (n=5) were evaluated as normal, 26.7% (n=16) as function loss and 46.7% (n=28) as scar + function loss. DMSA was not performed on 18.3% (n=11) of patients (Figure 2).

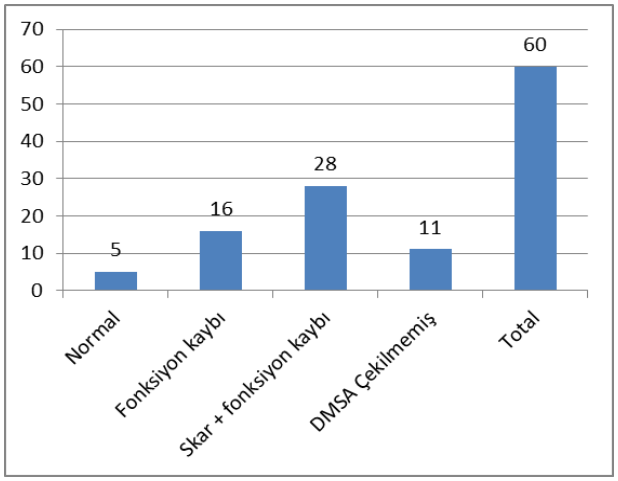

Figure2. Patients' preoperative DMSA results

Antibiotic prophylaxis was given to 78.3% (n=47) of patients before surgery in our center, while trimethoprim+sulfamethoxazole prophylaxis at 1-2 mg/kg per day was administered for various durations to 21.7% (n=13) of subjects.

No repeat surgery was required after surgical intervention in any case. Short-term surgical complications were observed in two cases. Blood pressure elevation was observed in two patients, and these received antihypertensive therapy. Hypertension was identified in the long term in one patient, and this was brought under control with antihypertensive therapy.

No previous surgical procedure had been performed in 81.7% (n=49) of cases. Subureteric injection had been performed in 18.3% (n=11). Distribution of the surgical procedures applied is shown in Table 3.

Table 3. Surgical techniques performed

Surgical technique	No.	%
Cohen UNC	32	53.3
Lich Gregoir	27	45
Politano Leadbetter	1	1,7

Postoperative VSUG or USG were performed on 32 (55%) patients. Lesion persisted as unilateral grade 2 in only 1 (1.7%) patient (with preoperative bilateral stage 4 VUR lesion). Due to absence of clinical symptoms at follow-up, no second intervention was required. Examination of postoperative urinary dysfunction revealed enuresis nocturna in 4 patients and urinary dribbling in one.

No significant association was determined between patients' degrees of VUR and age at diagnosis or age at surgery (p=0.682 and p=0.673, respectively) (Table 4).

Table 4. relations between VUR degrees and age at surgery and age at diagnosis of VUR

		No	Mean	SD	P
Age during VUR surgery (years)	**Grade 2**	6	76.67	38.960	0.68
	Grade 3	11	80.18	33.328	
	Grade4	23	68.43	33.451	
	Grade5	18	81.33	41.016	
	Total	58	75.52	36.013	
Age at diagnosis at VUR (year)	**Grade 2**	6	6.22	3.141	0.67
	Grade 3	11	6.45	2.885	
	Grade 4	23	5.59	2.726	
	Grade 5	18	6.74	3.488	
	Total	58	6.18	3.012	

SD, standard deviation

No statistically significant correlation was observed between patient gender and degree of VUR (p=0.859) (Table 5).

No statistically significant difference was observed between degree of VUR and preoperative urinary dysfunction (p=0.73) (Table6).

Table 5. Correlation between gender and degrees of VUR

VUR degree	Grade 2	Grade 3	Grade 4	Grade 5	p
Male	1	4	7	5	0.85
Female	5	7	16	13	

Table 6: Correlation between degree of VUR and preoperative urinary dysfunction

	No preoperative urinary dysfunction	Preoperative urinary dysfunction	p value
Grade 2	5	1	0.73
Grade 3	6	5	
Grade 4	15	8	
Grade 5	12	6	

Discussion

Although VUR generally appears as harmless and benign disease, it is still the main and most common cause of renal insufficiency in Turkey [14]. VUR must always be considered at differential diagnosis of recurrent UTI by pediatricians and other physicians concerned with childhood diseases [5]. Renal damage increases in line with degree of VUR [15,16]. Mean patient age and renal scarring levels were high in our study. We attribute this to inadequacies in the diagnosis and management of VUR. Previous studies have revealed a linear correlation between degree of VUR and renal parenchymal injury. Skooget al. [17] reported renal parenchymal injury in 5% of cases of grade 1 VUR, 6% of cases of grade VUR, 17% of grade 3 VUR and 50% of grade 5 VUR. Scar and function loss was determined at DMSA tests in a high number of patients, 74.3%, in our study. Low degree VUR has predominantly been determined in cases reported in previous studies.

However, some studies have also reported the exact opposite. In a study involving 398 cases, Tekgül et al. [18] identified renal scarring in 70.7% of patients at DMSA scintigraphy and reported that approximately 75% of patients were high grade VUR (grade 4-5). Similarly, in a study from Sudan, Ali et al. [7] reported that 64% of cases were advanced grade and exhibited renal injury. The degrees of reflux and renal scar levels in these two studies are similar to our own data. This may be associated with delayed age of diagnosis and suggests an effect of environmental and genetic factors.

A cause and effect relationship between UTI and VUR has been shown in the literature. The number of postoperative UTI attacks has been shown to decrease by 20% to 50% compared to before surgery [18]. In our study, too, some patients experienced up to 15 febrile and afebrile UTIs before surgery, these levels decreasing to 7 and 12 postoperatively. However, this was not statistically significant.

There are today serious doubts concerning the efficacy of prophylactic antibiotic use in patients with VUR for the purpose of preventing UTIs. National Institute for Health and Clinical Excellence (NICE) and American Pediatric Academy (APA) guidelines do not recommend the routine use of antibiotic prophylaxis in patients with VUR [19]. However, the European Association of Urology (EAU) does recommend the use of antibiotic prophylaxis in all children with VUR until they are toilet trained [18]. Only a very few of the patients in our study were started on prophylactic therapy. Since the majority of patients were diagnosed while being tested for non-specific reasons, or were diagnosed at external centers or referred during monitoring, prophylaxis data were not available for all patients. Patients among those known to have received prophylaxis underwent surgery because recurrent UTI could not be brought under control.

In contrast to much previous research, higher grade VUR was identified in our series. No significant correlation was determined between resulting renal injury and degree of VUR and gender. This may be attributable to the low case number. The most important factor responsible for resulting renal injury is more advanced patient age, the fact that most patients were diagnosed incidentally during investigation of UTI and that these patients were not monitored by one specific center and physician. VUR is more common in girls than boys among children undergoing urinary system investigation [7]. Similar data in terms of gender were also obtained from our study.

There is no consensus on whether medical treatment or surgery should be the treatment of choice in VUR [9-20]. While spontaneous improvement or complete resolution is seen in the majority of low grade cases, renal injury and renal scarring have unfortunately been reported in 4.7% and 23% of patients in the waiting period [21]. The higher patient age in our study supports this. Early endoscopy or laparoscopy or open surgery are as important as early diagnosis in cases receiving medical treatment after diagnosis and with appropriate indications [22]. The decrease in urinary dysfunction following surgery compared to before surgery in our study highlights the importance of treatment. The fact that complications developed in only two patients following treatment also suggests that surgery is a reliable option. Factor such as the low socioeconomic levels of the families in the region served by our hospital, transportation difficulties in reaching our center and insufficient attention to child care being shown by

families represent other obstacles to early diagnosis and patient monitoring.

The endoscopic approach is today regarded as the preferred surgical approach in the majority of patients. Ureteroneocystostomy is more important as a first treatment option in cases in which the endoscopic approach has been unsuccessful, and in which high grade (grade 4-5) reflux is accompanied by neurogenic bladder and additional pathologies (ureterocele, diverticulitis, ectopic ureteral orifice and duplex collecting system) [23]. In deciding on a surgical option, the most appropriate technique for the patient and that with which the surgeon is most familiar must be preferred. Patient compliance and family preference must also not be overlooked. The fundamental aim in open and laparoscopic techniques is to prevent reflux by increasing the submucosal distance of the ureter and to prevent urinary system infections leading to damage that may be difficult to reverse.

Conclusion

VUR and reflux nephropathy are among the most important causes of kidney failure in childhood. Early diagnosis and appropriate treatment will reduce potential renal injury to a minimum. Therefore, primary and all other physicians encountering children with recurring UTI must be aware of this and be properly informed concerning the treatment and monitoring of the disease.

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