

Original Article

Evaluation of the Clinical Findings of Pediatric Patients With Vesicoureteral Reflux to Assess Disease Severity


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ABSTRACT

Background and Aim: This study aims to investigate how to benefit from clinical and laboratory methods for further selection in the decision-making process to perform a cystogram and assess the severity of vesicoureteral reflux (VUR).

Methods: We retrospectively reviewed the voiding cystourethrography (VCUG), ultrasound (US), and medical records of pediatric patients with VUR. The exclusion criteria included having neurological lesions, a posterior urethral valve, and a lack of documentation of a renal ultrasound or voiding cystourethrography (VCUG). At the time of data entry, we retrieved demographic findings and laboratory test results, including routine biochemical parameters, complete blood count, and calculated blood sodium/potassium ratio

Results: Sixty-three pediatric patients with VUR were enrolled in this study. The mean (SD) age of the patients (female/male=37/26) at the time of diagnosis was 62.0±6.5 months (range 1-195 months). Seventeen patients (26.9%) had high-grade VUR, and 46 patients (73.1%) had low-to-moderate-grade VUR. The mean serum potassium level was significantly higher and the serum blood sodium to potassium (Na/K) ratio was significantly lower in the high-grade VUR group (4.7±0.5 vs. 4.3±0.4 mEq/L, P=0.022, 29±3 vs. 32±3, P=0.029, respectively) than the low-moderate group.

Conclusion: We conclude that the low serum sodium to potassium (Na/K) ratio allows us to predict the VUR grade. The effect of VUR on the renin-angiotensin-aldosterone system can be demonstrated by prospective controlled studies.

Keywords: Child, Kidney, Vesicoureteral reflux (VUR), Potassium

Introduction

Vesicoureteral reflux (VUR) is a crucial congenital urinary tract disorder in the pediatric age group with an estimated prevalence of 0.4%–1.8% [1]. Antenatal hydronephrosis and urinary tract infections are common causes to seek VUR [2]. Ten to twenty percent of newborns with antenatal hydronephrosis have VUR [3]. Venhola et al. [4] reported a prevalence of 28%–36% in children who underwent voiding cystogram due to presumed urinary tract infection (UTI). Vesicoureteral reflux is suggested as a risk factor for recurrent UTI and renal scarring [5]. Voiding cystourethrography (VCUG) has some disadvantages, such as being invasive, requiring patient preparation and catheterization, and causing exposure to ionizing radiation [6, 7]. Although technical advances have decreased the radiation dose to the patients by introducing low-dose fluoroscopy techniques, it is still required to perform a selective forecasting elimination process using clinical and laboratory examination. This study was conducted to investigate how to benefit from clinical and laboratory methods for further selection during the decision-making process to perform a cystogram and assess the severity of VUR severity.

Materials and Methods

We retrospectively reviewed the VCUG, ultrasound (US), dimercaptosuccinic acid (DMSA) findings, and medical records of pediatric patients who were followed up at Kırıkkale University hospital with a diagnosis of VUR between January 2011 and May 2021. At the time of data entry, we retrieved demographic findings, and laboratory test results, including routine biochemical parameters, complete blood count, and calculated blood sodium/potassium ratio.

According to ultrasonography, hydronephrosis was defined as a dilatation of the renal pelvicalyceal system [8]. According to the anterior-posterior diameter classification criteria, based on the pelvic diameter, it was graded as follows, mild hydronephrosis (7–9 mm), moderate hydronephrosis (10–15 mm), and severe hydronephrosis (>15 mm) [9].

A Urinary Tract Infection (UTI) was diagnosed if a child had positive nitrite and leukocyte esterase in a urine sample in the presence of typical symptoms, including fever, loin tenderness, frequency, dysuria, cloudy urine or hematuria, and a positive urine culture. Recurrent UTI was defined according to the national institute for health and care excellence (NICE) criteria [10].

Diagnosis of VUR was made by the demonstration of urinary reflux into the upper urinary tract by conventional VCUG. Grading of VUR was done according to the classification of the international reflux study group, including mild (grade 1–2), moderate (3), and severe (4–5) [11]. We compared low-moderate (VUR grade 1–3) and high-grade VUR (VUR grade 4, 5) groups concerning the means of clinical and laboratory variables.

The inclusion criteria included all pediatric patients with VUR. The exclusion criteria included having neurological lesions, posterior urethral valve, and lack of documentation of a renal ultrasound or VCUG.

Statistical analysis

Study data were analyzed by SPSS software v. 16.0. Statistical analyses were performed with the Chi-squared test and student's t test. Correlations between certain parameters were assessed by Pearson or Spearman's correlation analyses. The significance level was set at $P < 0.05$.

Results

Sixty-three pediatric patients with VUR were included in this study. The mean age of the patients (female/male=37/26) at the time of diagnosis was 62.0 ± 6.5 months (range 1–195 months). The proportion of female patients was higher than males (58.7% vs. 41.3%). The mean creatinine value of the patients was 0.44 ± 0.25 mg/dL (range 0.11–1.53 mg/dL) and the mean blood urea nitrogen (BUN) level was 21 ± 9 mg/dL (range 7–69 mg/dL).

Seventeen patients (26.9%) had high-grade VUR, and 46 patients (73.1%) had low-moderate VUR. No significant difference was observed between the high-grade VUR and low-moderate VUR groups regarding mean age, male gender ratio, history of recurrent urinary tract infection, mean hemoglobin (Hb), C-reactive protein (CRP), creatinine, BUN, albumin, and sodium levels (Table 1).

The mean serum potassium level was significantly higher and the serum blood sodium to potassium (Na/K) ratio was significantly lower in the high-grade VUR group (4.7 ± 0.5 vs. 4.3 ± 0.4 mEq/L, $P = 0.022$, 29 ± 3 vs. 32 ± 3 , $P = 0.029$, respectively) than the low-moderate group. Thirteen patients (20.6%) had additional anomalies. The low-grade VUR group had more additional anomalies (11 [23.9%] vs. 2 [11.7%]), such as horseshoe kidney ($n = 2$), ureteropelvic junction obstruction ($n = 4$), neurogenic bladder ($n = 3$), and ectopic kidney ($n = 2$).

Table 1. Comparison of demographic characteristics and laboratory parameters among two groups with vesicoureteral reflux (VUR)

Variables		Mean±SD/No. (%)		P
		High-Grade VUR n=17(26.9%)	Mild-Moderate Grade VUR n=46(73.1%)	
Age (month)		51±10	65±8	0.309
Gender	Male	7 (41.2)	19 (41.3)	0.992
Extra anomaly		2 (11.7)	11 (23.9)	
Horseshoe kidney		0	2	
Ureteropelvic junction obstruction		1	4	
Neurogenic bladder		1	3	
Ectopic kidney		0	2	
Severe hydronephrosis,		4(23.5)	35(76.5)	0.005*
Recurrent UTI		14(82.4)	43(93.5)	0.193
Hg (g/dL)		12.4±1.2	12.1±1.1	0.439
Mean CRP (mg/L)		30.3±9.3	18.8±4.9	0.292
Mean creatinine (mg/dL)		0.48±0.09	0.43±0.03	0.597
Mean BUN (mg/dL)		22±3	20±1	0.590
Albumin (g/dL)		4.3±0.4	4.5±0.5	0.156
Mean sodium (mEq/L)		139±4	138±3	0.341
Mean potassium (mEq/L)		4.7±0.5	4.3±0.4	0.022*
Mean serum Na/K		29±3	32±3	0.029*
Operated patients		8(47.1)	12(26.1)	0.049*

*P<0.05

Abbreviations: UTI: urinary tract infection; BUN: blood urea nitrogen; CRP: C-reactive protein; Hg: hemoglobin; Na/K: sodium to potassium.

The proportion of patients with severe anterior-posterior (AP) diameter dilation was significantly higher in the low-grade VUR group than in the high-grade VUR group (35[76.5%] vs. 4[23.5%], P=0.005).

No correlation was observed between VUR grade and mean creatinine, BUN, Na/K, hemoglobin (Hb), CRP, albumin, and anterior-posterior (AP) diameter (P=0.754, P=0.218, P=0.463, P=0.762, P=0.194, P=0.996, P=0.312, respectively).

Eight patients (47%) with high-grade VUR were operated on with Deflux® injection, while the corresponding rate was 26.1% in the low-grade VUR group. All six patients with grade 5 VUR underwent surgery. All operated patients with

low-grade VUR suffered from recurrent UTI despite the use of continuous antibiotic prophylaxis (CAP).

Discussion

Among patients with VUR, 10%–25% may develop the end-stage renal disease [12, 13]. In our study, only one patient (1.5%) with bilateral grade 5 VUR had a high creatinine level (1.53 mg/dL) in addition to a history of very frequent UTI. We think that after the diagnosis of VUR, judicious use of antibiotic prophylaxis is observed in our country.

Compared to the literature [14] reports, our patients were diagnosed with VUR at an older age. This can be explained by the tendency to avoid invasive procedures that have emerged for various reasons in recent years. Unlike previous studies, no difference existed in the mean gender of the high-grade VUR and low-moderate VUR groups [15, 16]. Previous studies have shown that boys had a greater degree of reflux and more often abnormal radiological findings. Our conflicting results may be due to regional differences.

Severe grades (grade 4-5) of reflux accounted for 26.9% of our patients. Similarly, Kurt-Sukur et al. [14] reported that 27.3% of subjects had high-grade reflux and Hannulo et al. [17] reported that around 20% of 2036 children had high-grade reflux.

We found a high rate of extra anomalies in unilateral VUR, such as ectopic kidney and horseshoe kidney. The literature data were consistent with our findings [18, 19]. Compound urinary tract abnormalities may increase the risk of renal impairment. To decrease the risk of a delayed renal injury, imaging studies, such as VCUG, CT scan, and radionuclide scan should be done, especially in pediatric cases where further urologic investigations are necessary.

Visible ureteral dilation has been associated with high-grade VUR [20]. A recent study recommended VCUG in patients with more severe APD or other abnormalities [21]. However, in contrast, we found no correlation between APD and VUR grade. This suggests that APD is not more indicative of high-grade VUR.

Surgical repair is indicated, especially in cases with persistent UTI despite the use of CAP. Moreover, persistent high-grade reflux, particularly if bilateral, and new renal scar formation are also the main indications for surgery [22]. Most patients with high-grade VUR (6/8) underwent surgery with the injection, and all patients with low-grade VUR who underwent surgery had a history of persistent recurrent infection despite the use of CAP.

The development of pseudohypoaldosteronism in obstructive uropathies, especially in infants, has been shown in various case reports in the literature. This relative increase in potassium in the severe VUR group may have appeared in the background of pseudo-hypoaldosteronism.

Similarly, Pumberger et al. [23] described 2 cases of VUR with transient pseudohypoaldosteronism. In another study [24], 6 infants with various urologic anomalies,

including VUR had hyponatremia and hyperkalemia. Plasma aldosterone concentration was markedly elevated, and plasma renin activity was similar to or higher than the normal level. In both studies, sodium and potassium levels returned to normal after medical or surgical therapy. Hence, our data indicating a relatively higher potassium level and lower blood Na/K ratio supported that hyperkalemic, salt loss can arise in children with VUR, especially those with high-grade VUR, as a result of tubular unresponsiveness to aldosterone.

Our study has some limitations, including the retrospective design, and a small sample size. Therefore, a follow-up study with a larger cohort is necessary.

Conclusion

In conclusion, a low blood Na/K ratio allows us to predict the VUR grade. The effect of VUR on the renin-angiotensin-aldosterone system can be demonstrated by prospective controlled studies. In this way, the severity and prognosis of VUR can be predicted from serum samples.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee approval for this study was obtained from the Clinical Research Ethics Committee of Kirikkale University (Date: 30.06.2021/decision no:2021.06.20).

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

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