

ORIGINAL PAPER

Significance of Sonographically Demonstrated Ureteral Dilatation in Evaluation of Vesicoureteral Reflux Verified with Voiding Urosonography in Children with Urinary Tract Infection

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ABSTRACT

Objectives. The aim of this study was to determine sensitivity, specificity, and predictive values of sonographically demonstrated ureteral dilatation in detecting vesicoureteral reflux (VUR). **Methods.** Ethical approval from the Ethical Committee of Clinical Center University of Sarajevo and parental consent were obtained for this prospective study involving 120 children with history of urinary tract infections (UTIs). Ultrasound examination included the evaluation of the urinary tract, with a special emphasis on evaluation of ureteral dilatation. Voiding urosonography (VUS) was carried out according to a standard protocol with the use of ultrasound contrast agent Sono Vue of second generation. Ureteral diameter greater than 3 mm was considered pathological. Proven VUR was graded into one of three stages. **Results.** Infectio tracti urinarii recidivans was referral diagnosis in the majority of patients. The average age of patients was 4.33 ± 3.88 years (from 2 months to 16 years of age). VUS findings were normal in 59 (49.2%), and pathological in 61 (50.8%) patients. Statistical analysis showed significant correlation between type and grade of VUR. Our data confirmed predominance of VUR in females and in children under the age of 5. Statistically significant correlation between ureteral dilatation and the existence of VUR was found, with relatively high sensitivity (67.2%), specificity (81.4%), and high positive (78.8%) and negative predictive value (70.6%), total diagnostic accuracy of 74.2% in detecting VUR, and significantly increased probability (20 – 25%) of detecting VUR in patients with sonographically confirmed ureteral dilatation. **Conclusion.** Sonographically confirmed ureteral dilatation can be used as a predictor of VUR in children with UTIs, and in combination with other predictors, might find a place in an evidence-based selective strategy in children with suspected VUR.

Key words: Vesicoureteral reflux; renal ultrasound; voiding urosonography VUS; ureteral dilatation.

1. INTRODUCTION

Urinary tract infection (UTI) is a common and significant pediatric problem. It has been estimated that 8% of girls and 2% of boys will have at least one episode of UTI by seven years of age (1). Vesicoureteral reflux (VUR), the retrograde flow of urine from the bladder to the ureter and renal pelvis, has been identified as a risk factor for the development of UTI; it is diagnosed in 20–30% of children with a first UTI (2,3). VUR is a common and significant urinary tract abnormality in children, and can lead to renal scarring with subsequent development of hypertension and chronic renal failure. Thus, in current medical practice, the timely detection and treatment of VUR is considered to be very important (4). Most cases of VUR are diagnosed during the first year of life

after occurrence of a urinary tract infection, in newborns with prenatal hydronephrosis and by screening children who have a first-degree relative with VUR. Voiding cystourethrography (VCUG) is the main diagnostic imaging modality for VUR, followed by radionuclide cystography (RNC). In the past few years, there had been many changes in guidelines for VUR evaluation, resulting in numerous increasingly sophisticated imaging algorithms which included ultrasonography (US) as an alternative radiation-free imaging option (5). Real breakthrough for US examination of VUR came with the availability of stabilized intravesical US contrast agents (USCAs) and development of contrast-enhanced sonographic reflux examination—voiding urosonography (VUS). After VUS is introduced, the number of VCUG in-

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vestigations can be reduced by over half and, consequently, a significant reduction of radiation exposure in children can be achieved (6).

The aim of our study was to determine sensitivity, specificity, and predictive values of sonographically demonstrated ureteral dilatation in detecting VUR verified with VUS.

2. METHODS

In this prospective study conducted during the period from June 2013 to June 2014 we included 120 children, aged from 2 months to 16 years, who had a history of laboratory confirmed urinary tract infections (UTI), one or more, and other inclusion criteria (sterile culture not older than seven days, signed consent for examination by at least one parent). All ultrasound examinations and VUS examinations were done by experienced radiologist at the Clinic of Radiology, Clinical Center University of Sarajevo, according to the standard protocol on GE Healthcare LOGIQ P6 Pro ultrasound machine, using 4-5.5 MHz convex probe and 7-12 MHz linear probe, in accordance with the widely accepted recommendations (6). All patients were subjected to three days of antibiotic prophylaxis (day before the examination on the day of examination and one day after the examination). Data protection was assured. Unique identification number was given to each patient, and it was used in all data analyses. The study protocol received ethical approval from the Ethical Committee of Clinical Center, University of Sarajevo. All data analyses were performed using SPSS software, version 16. Descriptive statistics (percentages, mean and standard deviation [SD]) were used to summarize demographic data. The chi-squared test was also used to evaluate the differences between nominal variables. Differences were considered significant when p values were < 0.05 . The discriminative capability of ureteral dilatation was determined by calculating sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values.

2.1. Ultrasound examination

Ultrasound examination was performed according to standard protocol in supine and prone position. It included examination of urinary bladder, ureteral orifice, kidneys and collective system, with a special emphasis on evaluation of ureteral dilatation. Ureteral dilatation was considered present if ureteral diameter was greater than 3 mm, or if the ureter was seen as hypoechoic tubular zone regardless of its diameter. Ureteral dilatation was considered as an indirect echomorphological sign of VUR.

2.2. VUS

During VUS examination contrast-specific harmonic imaging with mechanical index (MI) below 0.10 was used, in order not to break the micro bubbles of the second-generation USCA. Second-generation USCA, SonoVue (Bracco, Milan, Italy), was used in this study. SonoVue is a stabilized aqueous suspension of sulfur hexafluoride microbubble (SF6) with the phospholipids shell. Its application has to be careful and slow to minimize the destruction of microbubble contrast and reduce the deposition of the suspension. Examination begun by placing a catheter into the urinary bladder and its discharge, followed by filling the lumen of the bladder with saline in amount corresponding to half of the expected bladder capacity under ultrasound control, with the patient in a supine

position. Expected capacity of the bladder was accessed by following formula: expected bladder capacity = $(age+2) \times 30$ (7). Once the bladder was filled with saline, SonoVue was applied at the rate of 1ml per filling of the bladder. The diagnosis of VUR was determined by the presence of moving echogenic micro-bubbles from USCA in the upper urinary tract. The examination was continued during voiding to assess active vesicoureteral reflux. A postvoiding image of the bladder and renal fossae was obtained to assess postvoiding volume and reflux. Voiding cystogram were assigned a grade 0-3 according to grading system based on VUS examination with second-generation USCA findings:

- Grade 0 – indicates no VUR;
- Grade 1 – USCA in the ureter only;
- Grade 2 – USCA in the mildly to moderately dilated renal pelvis (AP diameter of pelvis is 5-10 mm with or without calyceal dilatation, or 10-15 mm without calyceal dilatation) and normal or mildly dilated ureter (≤ 5 mm);
- Grade 3 – USCA in a significantly dilated renal pelvis (AP diameter of pelvis > 10 mm) and in a dilated (wider and rounded) calyces, and in a dilated ureter (diameter > 5 mm), which can be tortuous (8).

3. RESULTS

During twelve-months prospective study a total of 120 children (100%), average age 4.33 ± 3.88 years (from 2 months to 16 years of age), were examined by ultrasound and VUS. Forty (33.3%) patients were boys (mean age, $3,35 \pm 3,49$ years; median age, 2 years; age range: 0.2-16 years). The mean age of the 80 (66.7%) girls was $4,83 \pm 3,99$ years (median age, 3 years; age range, 0.2-16 years) and was significantly higher from that of the boys ($p < 0.05$). Among children aged up to one year (16 patients) there were significantly more boys (11 or 68.75%) than girls (5 or 31.25%) ($p < 0.01$); among children older than one year (104 patients) there were significantly more girls (75 or 72.1%) than boys (29 or 27.9%) ($p < 0.01$). Infectio tracti urinarii recidivans was referral diagnosis in the majority of patients (42 or 35%), and it appeared more frequently than other diagnoses ($p < 0.01$). It is followed by VUR

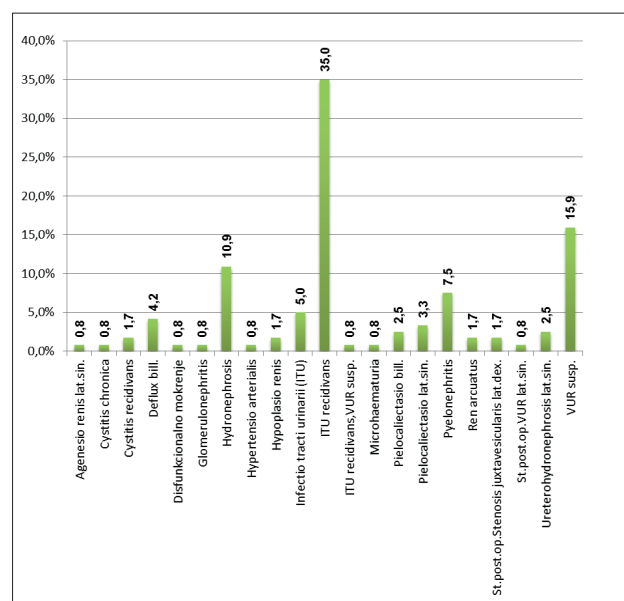


Figure 1. Distribution of referral diagnoses

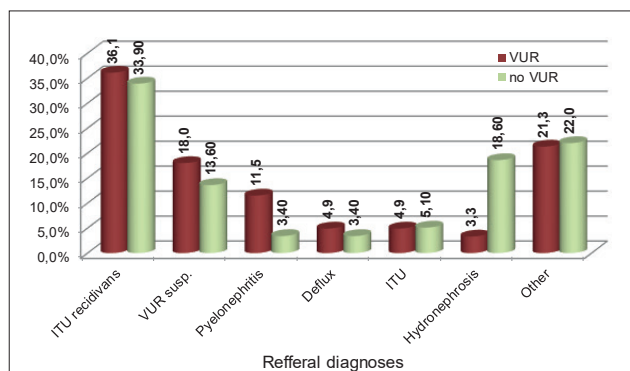


Figure 2. Distribution of refferal diagnoses of patients with and without VUR

VUS finding	Ureteral dilatation (US)		Total
	positive n (%)	negative n (%)	
Normal	11 (18.6%)	48 (81.4%)	59 (100%)
VUR – active	11 (64.7%)	6 (35.3%)	17 (100%)
VUR – passive	4 (40.0%)	6 (60.0%)	10 (100%)
VUR – active and passive	26 (76.5%)	8 (23.5%)	34 (100%)

Table 1. Relationship between VUR and sonographically demonstrated ureteral dilatation

susp. (19 or 15.9%) and hydronephrosis (13 or 10.9%). Other admission diagnoses were represented in less than 10% of cases as shown in Figure 1.

VUS findings were normal in 59 (49.2%), and pathological in 61 (50.8%) patients. From the total number of pathological VUS findings (61 patients), 34 or 55.7% were related to active and passive VUR, 17 or 27.9% to the active VUR, while the smallest number of patients, 10 or 16.4% of cases had the diagnosis of passive VUR. VUR – active and passive was detected significantly more often than other types of VUR ($p < 0.01$). Significantly higher percentage of patients with VUR (61 or 100%) had bilateral (28 or 45.9%) and left-sided VUR (27 or 44.3%), when compared to patients with right-sided VUR (6 or 9.8%) ($p < 0.01$). Of these 61 patients, 21 (34.5%) had grade 1 reflux, 2 (3.2%) had grade 1-2 reflux, 26 (42.6%) had grade 2 reflux, 3 (4.9%) had grade 2-3 reflux, and 9 (14.8%) had grade 3 reflux. Regarding VUR grade, significantly higher percentage of patients had VUR grade 1 and grade 2, when compared with patients who had higher VUR grades ($p < 0.05$). Statistical analysis showed statistically significant difference and correlation between type and grade of VUR ($p < 0.05$); lower VUR grades were detected more often in patients with active VUR, and higher VUR grades in patients with passive VUR and both active and passive VUR.

Average age of patients with VUR was $4,24 \pm 3,47$ years (median age, 3 years; age range: 0.2–14 years). Significantly higher number of patients with VUR were 1-5 years old, 34 of 61 patients (55.8%), compared to other age-related groups ($p < 0,01$); 5-10 years old (15 or 24.6%), up to one year (6 or 9.8%), and older than 10 years (6 or 9.8%). VUR was detected significantly more often in girls (41 or 67.2%), than boys (20 or 32.8%) ($p < 0,01$). Infectio tracti urinarii recidivans was referral diagnosis in the majority of patients with VUR, 22 of 61 patients (36.1%), and it appeared more frequently than other diagnoses ($p < 0.05$). It is followed by VUR susp. (11 or 18.0%) and pyelonephritis (7 or 11.5%), as shown in Figure 2.

Eleven patients with normal VUS finding and 41 patients

with diagnosed VUR had ultrasound finding of ureteral dilatation: in most cases ureteral dilatation was present in patients with both active and passive VUR (26 patients) (Table 1). Significantly higher number of patients with VUR had positive US finding of ureteral dilatation, 41 of 61 patients (67.2%), when compared to patients with negative finding (20 or 32.8%) ($p < 0,01$). Statistically significant correlation between this ultrasound parameter and the existence of VUR was observed (Figure 3), with relatively high sensitivity (67.2%), specificity (81.4%), and high positive (78.8%) and negative predictive value (70.6%), total diagnostic accuracy of 74.2% in detecting VUR, and significantly increased probability (20 – 25%) of detecting VUR in patients with US confirmed ureteric dilatation (LR+, 3.61; LR-, 0.40).

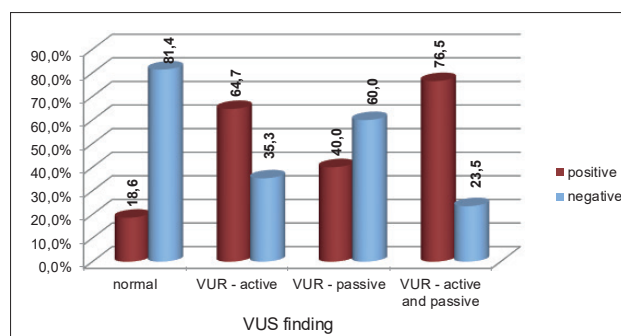


Figure 3. Correlation between US finding of ureteral dilatation (positive or negative) and VUR

4. DISCUSSION

The aim of our study was to determine sensitivity, specificity, and predictive values of sonographically demonstrated ureteral dilatation in detecting VUR verified with VUS. Conventional imaging modalities for diagnosing VUR include voiding cystourethrography (VCUG) and radionuclide cystography (RNC); both involve exposure to ionizing radiation (9,10). Ultrasound-based reflux imaging has been investigated in Europe for two decades; it is now a part of everyday clinical practice and incorporated into guidelines (11). In our country, Clinic of Radiology Clinical Center University of Sarajevo, introduced VUS as a part of diagnostic algorithms for VUR in 2012, and it was used in this study as a reflux imaging modality. VUS obviates exposure of children to ionizing radiation and allows prolonged, continuous scanning. The diagnostic accuracy of VUS in terms of reflux detection and grading has been evaluated in a number of comparative studies with VCUG; all those studies acknowledged high diagnostic accuracy of VUS (78-96%) (12,13,14). Furthermore, some studies revealed a higher sensitivity of the VUS harmonic imaging with a second-generation USCA compared to VCUG (15, 16). These results suggested echo-enhanced VUS as a method of choice when looking for VUR (Figure 4 and 5).

In our study, prevalence of VUR in children with a history of urinary tract infections was 50.8%, which is considerable compared to the similar studies (4,5,17,18,19,20); this confirmed the fact that of those children routinely presenting for investigation of reflux about half do not have reflux (10). Our finding demonstrates the importance of selection of patients that would very likely not have reflux on VCUG or RNC, thus eliminating unnecessary X-ray exposure. Giordano et

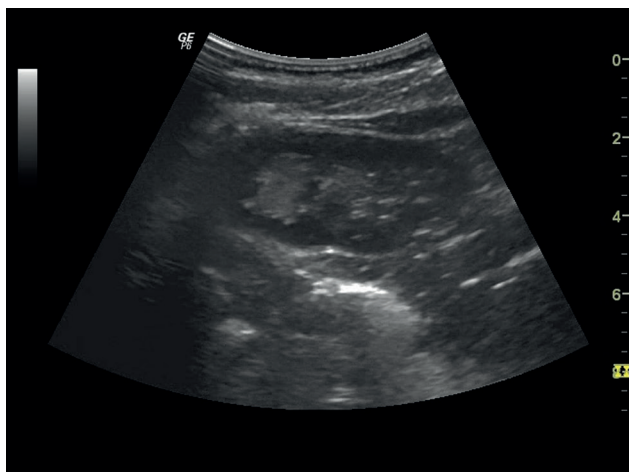


Figure 4. Presence of ultrasound contrast media in dilated pyelocaliceal system of the kidney is suggestive of VUR



Figure 5. Presence of ultrasound contrast media in distal ureter is suggestive of VUR

al. (2007) described 6-year experience with VUS used as a first step in the diagnosis of VUR, and concluded that VUS can be used as the first step in the diagnosis of VUR in children, boys and girls, with a significant reduction in radiation exposure (21). With the application of newer-generation USCA and ultrasound techniques, VUS is currently regarded as a valid, radiation-free imaging modality for examining vesicoureteric reflux (15). Our data confirmed significant predominance of VUR in females ($p < 0.01$) and in children under the age of 5 ($p < 0.01$), consistent with data from the literature (22-27). The severity or grade of VUR has been recognized as the main factor determining the likelihood of spontaneous reflux resolution and risk of renal injury. Higher grades of reflux are associated with decreased spontaneous resolution rates and increased prevalence of renal scars (28-30). Regarding VUR grade, significantly higher percentage of our patients had VUR grade 1 and grade 2, when compared with patients who had higher VUR grades ($p < 0.05$).

Given the existence of correlation between urinary infection and VUR (31), and taking into account that ultrasound remains part of the routine evaluation of first-time UTI in the pediatric population (32,33), we decided to analyze the usefulness of sonographically demonstrated ureteral dilatation obtained during routine ultrasound examinations of the urinary tract in detecting VUR. Statistically significant correlation between this ultrasound parameter and the

existence of VUR was observed, with relatively high sensitivity (67.2%), specificity (81.4%), and high positive (78.8%) and negative predictive value (70.6%), total diagnostic accuracy of 74.2% in detecting VUR, and significantly increased probability (20 – 25%) of detecting VUR in patients with US confirmed ureteric dilatation. Similar results were found in study by Leroy et al. (2010) and Kenney et al. (2002); authors concluded US measurement of the distal ureteral diameter is a useful additional tool in everyday assessment of children who might have reflux (34,35).

There are some limitations in our survey. The main limitation is that the sample size was restricted to 120 patients. Further, more comprehensive research is required in order to define the exact role of VUS as a valid alternative to VCUG in most clinical indications, based on its high efficacy, reliability, high safety profile and feasibility, and radiation safety for children. The timing of VUS after the diagnosis of UTI was variable; however, based on findings of other authors (36,37), it is highly unlikely that this influenced the rate of diagnosed VUR. The choice of thresholds for ureteral dilatation could be debated, as the literature has many discrepancies regarding the definition of this abnormality. Some radiologists performed both examinations; possible bias would probably be towards reporting more VUR in patients with positive ultrasound findings, which was not evident in the study results.

5. CONCLUSION

We concluded that US confirmed ureteric dilatation can be used as a predictor of VUR in children with UTI, and in combination with other predictors, might find a place in an evidence-based selective strategy in children with suspected VUR. Based on findings of this study, we may as well conclude that VUS harmonic imaging with a second generation contrast agent is far more superior method in detection of VUR compared to conventional ultrasound examination. VUR is emerging radiation-free reflux imaging modality that holds hope for future wider clinical application.

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CONFLICT OF INTEREST: NONE DECLARED

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