Relationship between ultrasound criteria and voiding ultrasonography (VUS) in the evaluation of vesicoureteral reflux (VUR)

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ABSTRACT

Aim To analyze the usefulness of five ultrasound parameters (ureteral dilatation, renal pelvis dilatation, renal parenchyma width reduction, calyceal dilatation, and urothelial reaction) in detecting vesicoureteral reflux (VUR).

Methods The study included 101 patients with diagnosed and therapeutically treated urinary infection. The ultrasound examination and voiding urosonography (VUS) were carried out according to a standard protocol. In the group of patients with proven VUR the presence of the indirect ecomorphological signs of VUR was evaluated.

Results The referral diagnosis urinary tract infection was present at the admission in 53 patients, while the remaining 48 patients were admitted with the diagnosis of infectio tractus urinarii recidivans. Pathological VUS was found in 53 patients. The ultrasound parameter with the highest sensitivity, specificity, and negative predictive value (77.4%, 79.2%, and 76.0%, respectively) in detection of VUR was urethral dilatation, while the parameter with the highest positive predictive value (62.5%) in detection of VUR was urothelial reaction.

Conclusion In case of ultrasound verification of ureteral dilatation or urothelial reaction, especially in if the urinary infection has proved, it is necessary to exclude the existence of VUR.

Key words: urinary tract ultrasound, ureteral dilatation, urothelial reaction
INTRODUCTION

Urinary tract infections are a common and significant problem in the pediatric population and if not recognized or inadequately treated they can lead to renal scarring with subsequent development of hypertension (1). Since the urinary infections are more frequent in the population of children with congenital malformations, the task of imaging methods is to establish the existence of this type of malformations (2). One of the most common urinary tract anomalies are the abnormalities related to the distal part of the ureter with subsequent development of vesicoureteral reflux (VUR). In 20-30% of children with the first acute urinary infection VUR is also present (3).

According to the National Institute for Health and Care Excellence (NICE) guidelines, ultrasound is the first diagnostic method used in the evaluation of children with diagnosed urinary infection, since it allows simultaneous detection of morphological changes that occur during the urinary infection and possible urinary tract abnormalities (4), while the voiding cystourethrogram (VCUG) is still the gold standard in definitive diagnosis of VUR (5). However, due to the fact that VCUG is a method which involves the use of ionizing radiation, voiding urosonography (VUS) has been increasingly used in evaluating VUR in recent years. The VUS is primarily used in the evaluation of VUR and according to leading experts it is considered practical, safe, relatively inexpensive, highly sensitive method, which does not use ionizing radiation; or in other words, a method closest to the ideal screening method for the VUR detection and grading (6,7).

The aim of our study is to analyze a predictive value of each of the five ultrasound parameters (ureteral dilatation, renal pelvis dilatation, renal parenchyma width reduction, calyceal dilatation, and urothelial reaction) in detection of VUR diagnosed with VUS.

PATIENTS AND METHODS

In this prospective study, conducted between March and November 2012, 101 children, aged 2 months to 16 years, who were therapeutically treated at the Pediatric Clinic of the Clinical Center of University of Sarajevo, for their first or repeated urinary tract infections were enrolled. The pediatrician, a subspecialist of pediatric nephrology with twenty years of clinical experience, diagnosed the presence of urinary tract infection in all enrolled patients based on clinical status, pathological findings of urinary sediment (microscopically detected bacteria in urine sediment or >20 leucocytes in urinary sediment or positive urinary culture), and pathological findings of blood analysis (CRP>20 mg/L; leucocytes>109/L).

Also, one of the criteria for enrolling in the study was the acquisition of three consecutively sterile urine cultures immediately following the conclusion of antibiotic treatment which lasted from seven to ten days. The day after receiving the third consecutive sterile urine culture, the patients were sent for ultrasound examination and VUS. Nineteen (18.8%) patients who received parenteral antibiotic treatment were hospitalized in the Pediatric Clinic, while the remaining 82 (81.2%) patients were treated with per oral antibiotics without the need for hospitalization.

Given that all the patients were minors, their parents gave written consents for the examination and inclusion in the study.

The ultrasound examination and VUS were conducted in a single act; immediately after the grey scale ultrasound examination, we proceeded with the VUS.

Exclusion criteria were the patients with incomplete laboratory evaluation, patients without three consecutive sterile urine cultures immediately following antibiotic treatment, patients with urinary tract operations (deflux - Endoscopic injection of Deflux gel around ureteral opening to create a valve function and to treat vesicoureteral reflux or classical surgical VUR corrections), with anomalies of number of kidneys (agenesia, cross-fused ectopia, ren arcuatus) with diagnosed glomerulonephritis, and patients with VUS proven bilateral VUR of different grade.

All ultrasound and VUS examinations were conducted by one experienced radiologist at the Clinic of Radiology, Clinical Centre University of Sarajevo. A prerequisite for performing routine gray scale ultrasound of urinary tract and VUS were sterile urine culture and signed consent for examination by at least one parent.
Ultrasound examination

Gray scale ultrasound examination of urinary tract was performed with routine protocol in supine and prone position. The appearance, shape, and thickness of the bladder wall were analyzed as well as the appearance and width of the ureteral orifice, appearance of ureter, longitudinal diameter of kidneys, appearance and width of renal parenchyma and appearance of calyceal system. The mandatory part of the examination was the estimation of urothelial appearance and thickness. Ureteral dilatation was present if the ureter was seen as a hypoechoic tube of any diameter, since the ureter should not normally be visualized during ultrasound examination (8).

Renal pelvis measurements were obtained at the widest section of the renal pelvis on transverse mid-kidney ultrasound images. Renal pelvis was considered dilated if its maximum width was over 5 mm (8). When assessing the renal parenchyma width, all values below 95% confidence interval (CI) for the age, were considered as reduced width of renal parenchyma (8).

Ultrasound visualization of calices was considered as a sign of caliceal dilatation since calices are not normally visualized during ultrasound examination (9).

Urothelial thickness was measured at the level of renal pyelon. The renal pyelon was imaged in transverse and longitudinal planes. A cut-off value of 2.0 mm was used to distinguish healthy urothelium from pathologically thickened urothelium (10). The expression urothelial reaction as a synonym for thickened urothelium was used.

Voiding urosonography (VUS)

All patients were subjected to three days of antibiotic prophylaxis (day before the examination and one day after the examination). Examination was started by placing a catheter into the lumen of the bladder and its discharge, after which the lumen of the bladder under ultrasound control was filled with saline. The expected capacity of the bladder was calculated using the following formula: \( C = (a + 2) \times 30 \). Once the bladder was filled with saline in the amount corresponding to half of the expected bladder capacity, the contrast agent (Sono Vue, Bracco, Milan, Italy) was applied in the amount of 1mL per filling of the bladder. It is the ultrasound contrast agent of the second generation consisting of 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 to reduce the deposition of the suspension. The diagnosis of reflux is established based on visualization of microbubble in the ureter and pelvis or collecting system. The examination was continued during miction to assess active vesicoureteral reflux.

Proven VUR was graded into one of three grades (11): grade 1 - contrast in the ureter; grade 2 - contrast in the ureter, pelvis and calyx, pelvis dilatation up to 10 mm, without dilated calix; grade 3 - contrast in the dilated pyelon over 10 mm, widened collecting system, compression on renal parenchyma.

Statistical analysis

Statistical analysis was performed by using a patient as a unit (two kidneys and two ureters were considered as a unit). The detection of unilateral or bilateral VUR was considered a positive or pathological VUS finding regarding the presence of VUR. The study did not include patients with diagnosed bilateral VUR of different grade. Research results are presented in tables by absolute numbers and percentages. Statistical analysis was performed by the Spearman rank correlation coefficient, bivariate logistic regression analysis, and the calculation of sensitivity, specificity, positive, and negative predictive value.

RESULTS

During the eight-month prospective study a total of 101 children, of which 68 (67.3%) were girls and 33 (32.7%) were boys, were examined by ultrasound and VUS.

The mean age of patients was 4.2±3.9 years: the youngest patient was 2 months old, while the oldest was 16 years old. In terms of age groups, the majority of children were 0-3 years (59, 58.4%), followed by patients aged 5-10 years (21, 20.8%), children aged 3-5 years (12, 11.9%), while the lowest number of children was older than 10 years (nine, 8.9%).

Referral diagnoses were evaluated only from the perspective whether it was the first or se-
cond *infectio tractus urinarii* (ITU), or the recurrent urinary tract infection *infectio tractus urinarii recidivans* (ITU recidivans). The majority of patients (53, 52.5%) were admitted with the ITU diagnosis, while the remaining patients (48, 47.5%) were admitted with the ITU recidivans diagnosis.

The VUS finding was normal in 48 (47.5%) patients, while pathological in 53 (52.5%) patients. Of the total number of pathological VUS findings the VUR was diagnosed in 38 (71.7%) girls, and 15 (28.3%) boys. Regarding the VUR grade, the largest number of patients with positive findings had grade 2 2.24 (41.5%), and the lowest number of patients had grade 1 to 2, which was present only in one patient (1.9%) (Table 1).

<table>
<thead>
<tr>
<th>VUR grade</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 (34.0)</td>
</tr>
<tr>
<td>1 - 2</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>2</td>
<td>22 (41.5)</td>
</tr>
<tr>
<td>2 - 3</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>3</td>
<td>9 (17.0)</td>
</tr>
<tr>
<td>Total</td>
<td>53 (100.0)</td>
</tr>
</tbody>
</table>

Positive family history regarding the presence of VUR was present in 15 patients with normal VUS finding, and in 17 patients with diagnosed VUR.

Ultrasound finding of renal parenchyma width reduction was noted in 13 patients with normal VUS finding, while renal parenchyma width reduction confirmed with ultrasound was present in eight patients with diagnosed VUR. The correlation between the aforesaid ultrasound parameter and existence of VUR was not observed (p>0.05).

Ten patients with normal VUS finding and 41 patients with diagnosed VUR had an ultrasound finding of ureteral dilatation. Statistically significant correlation (ρ=0.468; p=0.0001) between ureteral dilatation and VUR was observed.

Sixteen patients with normal VUS finding and five patients with diagnosed VUR had an ultrasound finding of calyceal dilatation. Though statistically significant correlation between calyceal dilatation and VUR has been observed, this ultrasound parameter showed low sensitivity (9.4%), relatively high specificity (66.6%), with low positive predictive value (23.8%), and mediocre negative predictive value (40.0%) for the occurrence of VUR (Table 2).

<table>
<thead>
<tr>
<th>Ultrasound parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchyma width reduction</td>
<td>38.1%</td>
<td>43.8%</td>
<td>15.1%</td>
<td>72.9%</td>
</tr>
<tr>
<td>Ureteral dilatation</td>
<td>77.4%</td>
<td>79.2%</td>
<td>30.3%</td>
<td>76.0%</td>
</tr>
<tr>
<td>Calyceal dilatation</td>
<td>9.4%</td>
<td>66.6%</td>
<td>23.8%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Renal pelvis dilatation</td>
<td>41.5%</td>
<td>37.5%</td>
<td>42.3%</td>
<td>36.7%</td>
</tr>
<tr>
<td>Urothelial reaction</td>
<td>56.6%</td>
<td>62.5%</td>
<td>62.5%</td>
<td>66.6%</td>
</tr>
</tbody>
</table>

PPV, Positive Predictive Value; NPV, Negative Predictive Value.

Thirty patients with normal VUS finding and 22 patients with diagnosed VUR had a positive ultrasound finding of renal pelvis dilatation. Statistical analysis did not show significant correlation between VUR and renal pelvis dilatation (ρ=0.116; p=0.222).

Ultrasound finding of urothelial reaction was positive in 30 patients with the diagnosis of VUR. This ultrasound finding was present in 18 patients with a normal VUS finding. Statistical analysis revealed the existence of a significant correlation between the presence of urothelial reaction and VUR (ρ=0.294; p=0.002) (Table 2).

By using regression analysis the odds ratio of each one of the five studied ultrasound parameters in the detection of VUR was evaluated (Table 3). Regression analysis indicated that from all observed ultrasound parameters (renal parenchyma width reduction, ureteral dilatation, calyceal dilatation, renal pelvis dilatation, and urothelial reaction) only ureteral dilatation can be considered as an independent ultrasound indicator of VUR (OR=11.456; p=0.0001).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio (OR)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Renal parenchyma width reduction</td>
<td>1.443</td>
<td>.511</td>
</tr>
<tr>
<td>Ureteral dilatation</td>
<td>11.456</td>
<td>.000</td>
</tr>
<tr>
<td>Calyceal dilatation</td>
<td>.248</td>
<td>.111</td>
</tr>
<tr>
<td>Renal pelvis dilatation</td>
<td>.699</td>
<td>.514</td>
</tr>
<tr>
<td>Urothelial reaction</td>
<td>1.564</td>
<td>.377</td>
</tr>
<tr>
<td>Constant</td>
<td>.383</td>
<td>.065</td>
</tr>
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DISCUSSION

In our study, VUS was used as a method for detecting VUR. Although this method has been used in developed countries in everyday clinical practice for many years, in 2012 the Clinic of Radiology (Clinical Center of the University of Sarajevo) in-
troduced this method in routine clinical practice. Previously, the diagnosis of VUR was made exclusively by VCUG, a method that involves the use of ionizing radiation. Due to the fact that ionizing radiation has accumulation effect and is used predominantly in the pediatric population, the introduction of VUS has even greater value.

Numerous recent studies have demonstrated high diagnostic accuracy of VUS which is in the range of 78-96% in detection of VUR in comparison with the conventional method, e.g., VCUG. As a conclusion of these results, VUS is increasingly becoming the primary imaging modality in the VUR evaluation. It is important to note that VUS is still not sufficiently accurate in the evaluation of urethra in boys (12).

Our data related to the predominance of VUR in girls is consistent with data from literature (13). Given the existence of correlation between urinary infection and VUR (14), and taking into account that ultrasound imaging is the first diagnostic method used in diagnostic algorithm for urinary tract infections in the pediatric population (4), we decided to analyze the usefulness of ultrasound criteria obtained during routine gray scale ultrasound examinations of the urinary tract in detecting VUR. A review of the available literature shows that a number of authors have analyzed the common overall sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound parameters indicative of the presence of VUR. They concluded that these parameters cannot be used in daily practice in detecting VUR due to low sensitivity and specificity, and low positive and negative predictive value (15,16). The results of our study indicate that ultrasound parameters such as reduction of renal parenchyma width, calyceal dilatation, and renal pelvis dilatation observed individually are not sufficiently sensitive and specific in detecting VUR, which is consistent with the results of other authors (15,16). Pyelocaliceal dilatation is most commonly a consequence of subpelvic stenosis which is primarily caused by congenenital aberrant vessels or fibrous bands and congenital ureteropelvic junction stenosis (17). The most common cause of renal parenchyma width reduction in pediatric patients is hydronephrosis. In this group of patients, the majority of cases of hydronephrosis is caused by anatomic abnormalities, including urethral valves or stricture, and stenosis at the ureterovesical or ureteropelvic junction (17). Since the renal pelvis dilatation, calyceal dilatation, and renal parenchyma width reduction are the characteristics of only high grade VUR (11), and the fact that in our research high grade VUR was detected only in minority of participants, the poor statistical correlation between those three ultrasound parameters and VUR was expected.

In the case of ureteric dilatation, we found a statistically significant correlation between this ultrasound parameter and the existence of VUR, with high sensitivity, specificity, and high positive, and negative predictive value. This result corresponds to the results found by Leroy et al. (8). The ultrasound parameter that we consider to be a possible indicator of the presence of VUR in our study was the urothelial reaction. According to the literature, urothelial reaction is the response to an acute or recurrent urinary tract infection. Urothelial reaction, or urothelium thickened, is the response to inflammation. It can be present in both acute or recurrent urinary tract infection and cannot be used to distinguish acute from chronic inflammation of the urothelium (10). Through reviewing the available literature, we could not find any study that analyzed correlation between this ultrasound parameter and the existence of VUR. In our study, we observed the existence of significant correlations between the presence of urothelial reaction and the presence of VUR. However, statistical analysis showed that the ultrasound parameter of urothelial reaction cannot be designated as a characteristic of VUR, given that the same is common finding in urinary tract infections that are not associated with the presence of VUR.

Our results suggest that among all five studied ultrasound parameters, ureteral dilatation is statistically the most significant predictor of VUR, followed by urothelial reaction, renal parenchyma width reduction, and renal pelvis dilatation respectively. In case of ultrasound verification of ureteral dilatation or urothelial reaction, especially in case of proven urinary infection, it is necessary exclude the existence of VUR.

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**TRANSPARENCY DECLARATION**

Competing interests: None to declare.
Odnos između ultrazvučnih kriterija i ultrazvučne mikcione cistografije (UMCG) u evaluaciji vezikoureteralnog refluxa (VUR)

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SAŽETAK

Cilj Analizirati korisnost pet ultrazvučnih parametara (dilatacija uretera, dilatacija šijelona, redukcija širine parenhima bubrega, kalicealna dilatacija i realcija urotela) u detekciji vezikoureteralnog refluxa (VUR). Metode U studiju je bio uključen 101 pacijent s dijagnosticiranom i terapeutski tretiranom urinarnom infekcijom. Ultrazvučni pregled i ultrazvučna mikcione cistografija (UMCG) uručeni su prema standardnom protokolu. U skupini pacijenata s dokazanim VUR-om analizirano je prisustvo indirektnih ehomorfoloških znakova VUR-a. Rezultati Uputna dijagnoza urinarni infekcija bila je prisutna kod 53 pacijenta pri prijemu, dok je ostalih 48 pacijenata primljeno pod uputnom dijagnozom infection tractus urinarii recidivans. Načelno UMCG-a bio je patološki kod 53 pacijenta. Ultrazvučni parametar s najvećom senzitivnošću, specifičnošću i negativnom prediktivnom vrijednošću (77,4%, 79,2% i 76,0%) u detekciji VUR-a bila je dilatacija uretera, dok je parametar s najvećom pozitivnom vrijednošću (62,5%) u detekciji VUR-a bila reakcija urotela. Zaključak U slučaju ultrazvučno verificirane dilatacije uretera ili reakcije urotela, osobito ukoliko je dokazana urinarna infekcija, neophodno je isključiti postojanje VUR-a.

Ključne riječi: ultrazvuk urotrakta, dilatacija uretera, reakcija urotela

REFERENCES