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 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-
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 hypechoic tubular zone regardless of its diameter. Ureteral dilatation was considered as an indirect echo-morphological 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) x 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 pelvis 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 ± 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 ± 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...
Significance of Sonographically Demonstrated Ureteral Dilatation

Table 1. Relationship between VUR and sonographically demonstrated ureteral dilatation

| 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 2. Distribution of referral diagnoses of patients with and without VUR

Referred diagnoses

| VUS finding | US finding of ureteral dilatation (positive or negative) | n (%) | Total |
|-------------|--------------------------------------------------------|-------|-------|
|             | 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%) |

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

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 cystourethography (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 (79-96%) (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.
Significance of Sonographically Demonstrated Ureteral Dilatation

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. Same 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.

Acknowledgments

We convey our special thanks to Pediatric Clinic, Clinical Center University of Sarajevo, Clinic of Radiology, Clinical Center University of Sarajevo and study participants.

CONFLICT OF INTEREST: NONE DECLARED

REFERENCES

1. White B. Diagnosis and treatment of urinary tract infections in children. American Family Physician. 2011; 83(4): 409-415.
2. Williams G, Fletcher JT, Alexander SI, Craig JC. Vesicoureteral reflux. J Am Soc Nephrol. 2008; 19(5): 847-862.
3. Sargent MA. What is the normal prevalence of vesicoureteral reflux? J Am Soc Nephrol. 2008; 19(5): 847-862.
4. Pohl GH, Joyce FG, Wise M, Cilento Jr GB. Pediatric Urologic Diseases. In Litwin MS, Saigal CS (eds.) Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: Government Printing Office, 2007: 379-418.
5. Weinberg AE, Hsieh MH. Current management of vesicoureteral reflux in pediatric patients: a review. Pediatric Health,
Significance of Sonographically Demonstrated Ureteral Dilatation

6. Darge K. Voiding urosonography with ultrasound contrast agents for the diagnosis of vesicoureteral reflux in children. Pediatric Radiology. 2008; 38:40-53.

7. Koff SA. Estimating bladder capacity in children. Urology. 1983; 21: 248.

8. Ključevšek D, Battelino N, Tomažič M, Kersnik Levart T. A comparison of echo-enhanced voiding urosonography with X-ray voiding cystourethrogram in the first year of life. Acta Paediatrica. 2012; 101(5): 235-239.

9. Perisinakis K, Raisakis M, Damilakis J, Stratakis J, Neratzoulakis J, Gourtsoyiannis N. Fluoroscopy-controlled voiding cystourethrography in infants and children: are the radiation risks trivial? Eur Radiol. 2006;16: 846-851.

10. Darge K. Diagnosis of vesicoureteral reflux with ultrasonography. Pediatric Nephrology. 2002; 17(1): 52-60.

11. Darge K, Gratten-Smith JD, Riccabona M. Pediatric uroradiology: state of the art. Pediatr Radiol. 2011; 41: 82-91.

12. Darge K. Voiding urosonography with US contrast agent for the diagnosis of vesicoureteric reflux in children: an update. Pediatric Radiol. 2010;40(6): 956-962.

13. Ji LN, Cao L, Chen DK, Cui YC, Zhang YL, Ye H, Hao CS, Yuan XY. Evaluation of the clinical and imaging examinations in high-risk children with vesicoureteral reflux. Zhonghua Er Ke Za Zhi. 2011; 49(4): 282-286.

14. Mentzel HJ, Vogt S, John U, Kaiser WA. Voiding urosonography with ultrasonography contrast medium in children. Pediatr Nephrol. 2002;17(4): 272-276.

15. Papadopoulou F, Anthopoulos A, Siomou E, Efremidis S, Tsiamboulas C, Darge K. Harmonic voiding urosonography with a second-generation contrast agent for the diagnosis of vesicoureteral reflux. Pediatr Radiol. 2009; 39(3): 239-244.

16. Kes E, Nyitrai A, Várkonyi I, Máttyus I, Cseprekál O, Reusz G, Szabó A. Voiding urosonography with second-generation contrast agent versus voiding cystourethrogram. Pediatr Nephrol. 2010 Nov; 25(11): 2289-2293.

17. Sargent MA. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol. 2000; 30: 587-593.

18. Yoshinaga A, Morozumi M, Yamashita T, Ishii N, Matsuda T, Terao T, Hayashi T, Yamada T. Prevalence of hydronephrosis and vesicoureteral reflux in pediatric urinary tract infection. Hinyokika Kiyo. 2007; 53(10): 691-693.

19. Abhamsam I, Al Harbi A, Fakheh K, Al Banyan E. The value of renal ultrasound in children with a first episode of urinary tract infection. Ann Saudi Med. 2009; 29(1): 46-49.

20. Cleper R, Krause I, Eisenstein B, Davidovits M. Prevalence of vesicoureteral reflux in neonatal urinary tract infection. Clin Pediatr (Phila). 2004; 43: 619-625.

21. Giordano M, Marzolla R, Puteo F, Scianaro L, Caringella DA, Depalo T. Voiding urosonography as first step in the diagnosis of vesicoureteral reflux in children: a clinical experience. Pediatric Radiol. 2007; 37(7): 674-677.

22. Novljan G, Kenig A, Rus R, et al. Cyclic voiding urosonography in detecting vesicoureteral reflux in children. Pediatric Nephrology. 2003; 18: 992-995.

23. Sharbf FG, Fallahzadeh MH, Modarresi AR, Emaeili M. Primary vesicoureteral reflux in Iranian children. Indian Pediatr. 2007; 44(2): 128-130.

24. Wadie GM, Tirabassi MV, Courtney RA, Moriarty KP. The reflux procedure reduces the incidence of urinary tract infections in patients with vesicoureteral reflux. J Laparoendosc Adv Surg Tech A. 2007; 17(3): 353-359.

25. Grebeldinger S, Radojičić B, Melnjikov I, Balj S. Modaliitet lećenja vezikoureternog refluksa kod dece. Vojnosanitetski pregled. 2009; 66(3): 388-394.

26. Mahant S, Friedman J, MacArthur C. Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. Arch Dis Child. 2002; 86(6): 419-420.

27. Chand DH, Rhaodes T, Poe SA, Kraus S, Strife CF. Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. J Urol. 2003; 170(4 Pt 2): 1548-1550.

28. Ajdinić B, Jauković I, Krtić Z, Đopuda M. Impact of micturating cystourethrography and DMSA renal scintigraphy on the investigation scheme in children with urinary tract infection. Adv Urol. 2008; 22(8): 661-665.

29. Tepmongkol S, Chotipanich C, Sirisalipoch S, Chaiwatanarat T, Vilaichon AO, Wataana D. Relationship between vesicoureteral reflux and renal cortical scar development in Thai children: the significance of renal cortical scintigraphy and direct radionuclide cystography. J Med Assoc Thai. 2002; 85 Suppl 1: S203-S209.

30. Zaffanello M, Franchini M, Brugnara M, Fanos V. Evaluating kidney damage from vesico-ureteral reflux in children. Saudi J Kidney Dis Transpl. 2009; 20(1): 57-68.

31. Dave S, Khoury AE. Diagnostic Approach to Reflux in 2007. Adv Urol. 2008: 367320.

32. Riccabona M, Avni FE, Blickman JG, et al. Imaging recommendations in paediatric uroradiology: minutes of the ESPR working group session on urinary tract infection, fetal hydronephrosis, urinary tract ultrasonography, and voiding cystourethrography, Barcelona, Spain, June 2007. Pediatr Radiol. 2008; 38: 138-145.

33. Lim R. Vesicoureteral reflux and urinary tract infection: evolving practices and current controversies in pediatric imaging. American Journal of Roentgenology. 2009; 192(5): 1197-1208.

34. Leroy S, Vantalon S, Larakeb A, Ducou-Le Pointe H, Bensman A. Vesicoureteral reflux in children with urinary tract infection: comparison of diagnostic accuracy of renal US criteria. Radiology. 2010; 255(3): 890-898.

35. Kenney IJ, Negus AS, Miller FN. Is sonographically demonstrated mild distal ureteric dilatation predictive of vesicoureteric reflux as seen on micturating cystourethrogram? Pediatr Radiol. 2002; 32(3): 175-178.

36. Mahant S, To T, Friedman J. Timing of voiding cystourethrogram in the investigation of urinary tract infections in children. J Pediatr. 2001;139(4): 568-571.

37. McDonald A, Scrannt M, Gillespie R, Mahajan V, Edwards GA. Voiding cystourethromgrams and urinary tract infections: how long to wait? Pediatrics. 2000; 105(4): E50.