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The Role of Contrast Enhanced Voiding Urosonography in Evaluation of Pediatric Urinary Tract Infection and Antenatal Hydronephrosis

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Abstract

Introduction: 30-50% of children presenting with urinary tract infection (UTI) as well as 8-38% of children diagnosed with antenatal hydronephrosis (ANH) have vesicoureteric reflux (VUR). The standard technique for the diagnosis of VUR is voiding urethrocystrogaphy (VCUG); however, it is associated with ionizing radiation. Contrast-enhanced voiding ultrasonography (ceVUS) is an alternative, radiation-free method with sensitivity and specificity in the diagnosis of VUR comparable with VCUG respectively, and with the ability to depict the structure of the urethra.

Aim: The aim of this article is to present our experience with ceVUS and to discuss its clinical indications in the context of the actual guidelines for the management of UTI in children and ANH.

Material and Methods: 118 ceVUS studies (236 nephroureteral units) performed in the period October 2016 to December 2017 were reviewed. 67 of patients were females and 51 males; the median age was 3.2 years, range: 1 month-18 years.

Results: VUR was shown in 62 (52.5%) children in 97 (41%) nephroureteral units. The urethra was shown in 90 (76%) children without significant pathology, except spinning top urethra found in 9 girls. Adverse events related to the examination were not reported, except one iatrogenic UTI.

Conclusion: In imaging of children presenting with UTI and ANH, ceVUS is an important radiation-free method for detection of VUR and evaluation of urethra. It is an acceptable alternative for radiation-associated VCUG in most clinical instances and should be incorporated into the imaging protocols of pediatric UTI and ANH.

Keywords: Vesicoureteric reflux; Urinary tract infection in children; Antenatal hydronephrosis; Voiding uretrocystography; Contrast-Enhanced voiding urosonography

Introduction

Primary VUR is one of the most frequent congenital anomalies in the childhood. The exact incidence is not known, because most patients are asymptomatic however the supposed prevalence in healthy population is around 1-2%. In children with symptomatic UTI, VUR is present in 30-50% and in children diagnosed with antenatal hydronephrosis in 8-38%, respectively [1-4]. In many patients VUR is not only anatomic anomaly of the ureterovesical junction due to shortening of the submucosal tunnel "*per se*" but there is coexisting functional bladder problem initiating and /or perpetuating reflux [5].

For years it has been believed that VUR in combination with UTI and intrarenal reflux lead to renal parenchymal damage known as reflux nephropathy (RN) [2]. However, this relationship has been challenged by several studies. It has been demonstrated that population of children with reflux nephropathy is not homogenous. In one group consisting of predominantly males with high grade VUR, RN is congenital, developing itself as result of embryological abnormality (renal dysplasia). Congenital RN has been reported in 30% to 60% of mostly male children with VUR diagnosed as a result of antenatally diagnosed hydronephrosis, also called prenatal VUR [4,6-8]. In the second group consisting predominantly of females, RN is an acquired condition associated with recurrent UTI, appearing mainly in the early childhood when the growing kidney parenchyma is more susceptible to the effect of reflux and infection. In patients with UTI and VUR. The reported incidence of RN varies from 36% to 56%. Children and adults with pyelonephritic renal scarring are at risk of serious long-term complications, e.g. hypertension, proteinuria and renal failure. Modern paediatric care, with early detection and treatment of urinary tract infections and reflux during childhood and adolescence, may improve long-term prognosis.

Traditional method for diagnosis of VUR accepted as gold standard is voiding cystourethrography (VCUG). VCUG allows precise delineation of anatomic details in the bladder and urethra, providing diagnosis and grading of VUR and diagnosis of distal urinary tract pathology. However VCUG is associated with exposure to ionizing radiation [9]. The mean radiation dose during VCUG is approximately 0.5 to 3.5 mSv [10]. It is equivalent to radiation dose of 25-160-number of X chest rays. The use of grid-controlled variable-rate pulsed fluoroscopy reduces effective radiation dose by eightfold, compared with older continuous fluoroscopy machines, however there is still

associated significant radiation and the modern machines are not always available.

Ordering physicians should be aware of the risk of radiation exposure arising from diagnostic radiological procedures used in childhood. It is considered that it can be connected with higher risk of cancer disease. In the study of large group of patients undergoing repeated CT scans was shown that cumulative doses of about 50 mGy might almost triple the risk of leukemia and doses of about 60 mGy might triple the risk of brain cancer. These doses are equivalent to 50-60 mSv of X-ray radiation [10,11]. In comparison with adults children are even more susceptible to the long-term effects of radiation mainly due to the increased radiation sensitivity of immature growing organs. Additionally children's life expectancy is longer and consequently there is a greater chance potential oncogenic effect of radiation to be manifested. Concern about the radiation exposure during VCUG is due to the many radiosensitive organs and tissues located in the field of radiation, including the gonads where the genetic potential is placed [9]. In imaging strategies especially in children it is recommended to keep radiation doses as low as reasonably achievable (ALARA principle) [9,11-12]. Radiation associated investigation should always be justified and performed only if they contribute to the therapeutic and/or prognostic decisions.

The contrast-enhanced voiding urosonography (ce-VUS) using second generation ultrasound agent, is a relatively new reliable and accurate method for diagnosis and staging of VUR and evaluation of urethra, with the great advantage of lacking radiation. Nevertheless, it is not still widely accepted method by the imaging community. Limitation to popularizing the method was the lack of approval for use in pediatric patients, necessitating off-label usage; however, the U.S. Food and Drug Administration (December 2016) and the European Medicines Agency (June 2017) recently approved a US contrast agent, sulfur hexafluoride lipid–type A microspheres, for the study of the pediatric urinary tract to detect VUR in the United States (Lumason; Bracco Diagnostics, Monroe Township, NJ) and Europe (SonoVue; Bracco, Milan, Italy) [13]. Despite the fact that the contrast agent has not been registered there are numerous reports worldwide describing ce-VUS in pediatric patients with intravesical administration of SonoVue [14-23]. ceVUS has been incorporated in the joint guideline for urological examination by the European Society of Urogenital Radiology [ESUR] and European Society of Pediatric Radiology (ESPR) [24,25], but it is not still incorporated into the American Academy of Pediatrics guidelines for management of UTI neither in correspondent guidelines of American Academy of family physicians nor in NICE guidelines, respectively [26-28].

The unique of our study compared to other studies discuss the same issue is the focus on clinical value of ceVUS and its potential role in management of children with UTI and ANH, in context of the actual guidelines.

Material and Methods

We reviewed ceVUS studies performed at our Hospital since October 2016 to December 2017. During this period 118 ceVUS in 236 nephroureteral units (NUUs) were performed. 67 patients were females and 51 males. Mean age was 3.2 years, range: 1 month-18 years. In 62 children indication for ceVUS was UTI, in 20 hydronephrosis and/or small kidney and in 36 ceVUS was performed as follow-up investigation in previously documented VUR.

The technique itself corresponds to that used in VCUG and it was described in detail in our previous report [29]. Through the catheter it has been infused into the bladder 0.5 ml second generation ultrasound agent SonoVue diluted in 250 ml saline in infants or 1 ml SonoVue/ 500 ml saline in older children, respectively. We begin by observing bladder filling, advance to alternating between the bladder and kidneys during filling and voiding phases using sagital and transversal view. In the renal study, we are especially careful to detect presence of microbubbles of contrast material in the pyelocaliceal system and ureters. This finding is diagnostic for VUR and to grade it, we used the five-level grading system adapted to VUS [17].

First voiding was carried out with the catheter left in the bladder. Usually several cycles were performed. The last voiding without catheter is most important for proper evaluation of the urethra. To evaluate the urethra, we use a transperineal approach, placing the probe in the sagital plane in all boys and we also use a suprapubic approach in infants and in a case of urgent voiding. A transpelvic approach was used for the study of the urethra in girls. Urethra is considered normal when we see adequate distention and normal caliber along its entire length.

The whole study was digitally recorded and stored on a hard drive and is available for review. The examinations were performed using Voluson E6 (GE Healthcare) ultrasound machine with a convex probe (2-5 MHz) , equipped with harmonic option and contrast specific software.

In order to minimize the breakage of microbubbles the mechanical index (MI) setting ranged between 0.04 and 0.1 in the low-MI contrast specific mode. To prevent catheter associated UTI all children received cefixime 8 mg/kg for 3 days, including the day of the examination. Any adverse events observed during the next 24 hours by phone reported by the parents were recorded.

Results

VUR was shown in 62 (52.5%) children in 97(41%) NUUs. It was unilateral in 47 and Bilateral in 25 children. In 52 NUUs VUR was grade II/V in 26 Grade III/V, in 16 grade IV/V and in 3 grade V, respectively. Urethra was shown in 90 (76%) children and in all boys, without major pathological finding. In 9 girls spinning top urethra was shown (Figure 1). Subsequent urodynamic studies performed in 5 of them, revealed functional bladder problem.

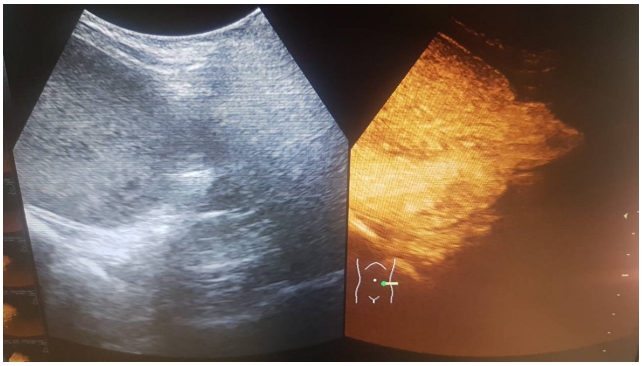

Figure 1: 6 years old girl with recurrent UTI - Spinning top urethra shown by ceVUS indicates functional bladder problem.

In the vast majority of examinees there were no any adverse events. Only in one, 3 month old girl, with diagnosis of bilateral high grade VUR (Figure 2) as complication of the catheterization acute pyelonephritis occurred with need for hospitalization. Three children manifested more expressed painful dysuria, but no infection.

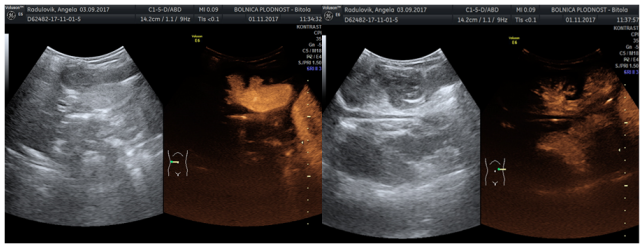

Figure 2: 3 months old girl with bilateral ANH - Bilateral high grade VUR, shown by ceVUS and intrarenal reflux on the left side.

Discussion

VCUG major indications in childhood include UTI and antenatal hydronephrosis. Therefore we should consider current evidence on these subjects. The American Academy of Pediatrics (AAP) recommendations for imaging after initial UTI from 1999 [26] included, renal and bladder ultrasound (RBUS), VCUG or radionuclide cisternography in all children up to 2 years old. This "*bottom-up*" strategy was intended to detect VUR, believing that there is causal relationship between VUR, kidney infection and subsequent renal scaring. However it has been shown that many children with pyelonephritis did not have VUR.

The "*top-down approach*" focuses on identifying children at risk for renal scarring, whether or not VUR is present. In this approach DMSA scintigraphy replaces VCUG as a first line investigation [27]. The intention is by DMSA to detect acute pyelonephritis, renal dysplasia, or acquired renal scarring and to perform VCUG in only patients with renal lesions. This approach provides diagnosis of only clinically significant VUR [1,27]. Both approaches employ ionizing radiation to image the urinary tract. Many research studies have been done with an idea to find how to reduce safely the amount of imaging and radiation exposure in children with UTI, without omitting the detection of those with a risk for renal scarring.

In the past period a range of approaches have been promoted that are changing in short periods. Most of them are more restrictive than previous ones, with shift away from invasive procedures and those with a substantial radiation burden (as VCUG). However, there is no universally accepted protocol. The NICE guidelines published in 2007 discourage routine imaging of all children after a first UTI [28]. RBUS is reserved for only atypical or recurrent UTI or for children less than 6 months of age. DMSA is recommended only in children less than 3 years of age with atypical or recurrent UTI and it is performed 4-6 months after UTI.

Revised APP guideline from 2011 [30], recommends that initial febrile UTI in children aged from 2 to 24 months, should begin with renal and bladder ultrasound. VCUG should be considered only if there were abnormalities on RBUS (e.g. hydronephrosis, suspected scarring or high-grade VUR), or after second febrile UTI. The recommendation for limiting VCUG in NICE and AAP guidelines was based on the assumption that majority of children with renal scaring do not have acquired lesion but had congenital renal hypo-dysplasia and that antibiotic prophylaxis was not effective. Compared to the past approach this recommendation provoked broad discussion and some confusion among the ordering physicians [1,31].

Ultrasound remains widely recommended as a safe noninvasive procedure. However, as much as 60% of reflux and 50% of renal scan abnormalities noted on DMSA are routinely missed by sonography [1]. At least some physicians were concerned that if they strictly follow the new guidelines they could miss the diagnosis of significant abnormalities and the gold opportunity to prevent renal damage. Some of them worry that the guidelines are promulgated to reduce overall costs rather than put patients first. We should remind that in the time when the new AAP and NICE guidelines were promoted the results of RIVUR study [32] were not still known. Published in 2014, RIVUR trial showed that antimicrobial prophylaxis was associated with a reduced risk of recurrence by 50% and reconsideration of that recommendation has been suggested. Existing confusion and dilemmas have led to the insufficient adherence to the guidelines and significant shortcomings in the implementation [33-35].

The second most frequent indication for VCUG in childhood is antenatal hydronephrosis. It has been recognized more often with widespread use of prenatal ultrasound screening. The prevalence of ANH is 0.6-5.4% and VUR is present in 8-38% of these children [36,37]. In the growing population of children with ANH clinically is important to distinguish those who have transitory hydronephrosis and thus need minimum investigation, from those who have more serious problem, requiring long-term follow up or surgery [38]. Recommended imaging strategy depends of the finding on postnatal ultrasound scan performed in the first week of age and repeated scan after 4-6 weeks. VCUG is recommended only in children with moderate to severe hydronephrosis (SFU grade 3-4, or renal APD 10 mm), and if dilated ureters, or bladder/ urethral abnormalities are present by ultrasonography [38]. In neonates with suspicion for distal urinary tract obstruction cystographic study should be done early, within first week of life. Otherwise it can be delayed and performed at 4-6 weeks of age. In addition, VCUG is also required in children with milder ANH grades, who show worsening hydroneprhosis, progressive parenchymal thinning or occurrence of UTI [38]. However, many research studies and reviews have suggested no correlation between severity of ANH and reflux grade and children with VUR may have normal postnatal ultrasound [36-40]. By following this recommendation diagnosis of significant VUR can be missed at least in some patients (Figure 3).

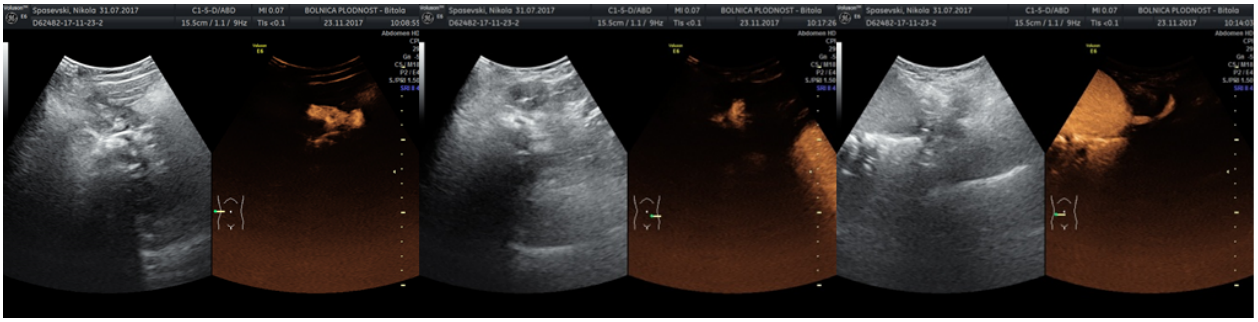

Figure 3: 2 months old boy diagnosed with left side ANH (SFU grade 2) - Bilateral VUR grade 3/5 was shown by ceVUS and normal urethral morphology.

It should be emphasized that all aforementioned guidelines on management of pediatric UTI or ANH, include conventional VCUG as a method of choice in imaging protocols. We hypothesize that the principle of radiation exposures as low as reasonably achievable was a concern in designing restrictive guidelines and complicated protocol algorithms.

We consider that if corresponding to VCUG but radiation free method was available the guidelines would not be so restrictive and many clinical dilemmas would be redundant. Clinicians will have an opportunity to use the guidelines non dogmatically, with more flexible and individualized approach. In our opinion individualized approach is especially important in children up 2 years, because of greater risk for renal damage characteristic for growing kidneys.

Search for radiation free cystographic method by using ultrasound has been initiated since the mid-1970s [14,41-42]. However only after introduction of stabilized ultrasound contrast agent on intravesical application as well as with advances in the ultrasound techniques, namely harmonic imaging and subtraction technique, preconditions were accomplished for development of technique with diagnostic performance comparable to VCUG, respectively.

First ultrasound contrast agent employed in ceVUS was Levovist [14]. Since 2011 it has been replaced with the more sophisticated second generation ultrasound agent SonoVue [15]. Sonovue is a preparation of stabilized microbubbles containing sulfur hexafluoride gas. Its characteristics to remain stable up to 6 hours provides the examinator with enough time to complete the investigation without risk of premature destroying of the contrast. In our study, we used 0.5 ml sonovue diluted in 250 ml saline in infants and 1 ml sonovue/ 500 ml saline for older children, respectively. In dependence of the age of patients we used one 5 ml vial of sonovue for investigation of at least 5 children, usually 7-8, and maximum 10 children respectively, that contributed to the lower cost of the examination.

The most important advantage of ceVUS vs. VCUG is that it does not involve ionizing radiation. The additional advantage is its dynamic character allowing not only anatomical information but real-time assessment of voiding function also. VUR is diagnosed if in contrast-harmonic mode microbubbles appear in the ureter or pelvicaliceal system [17-19]. For graduation the classification system similar to the wide world used international classification, adapted for VUS by Darge & Troeger was applied [17]. Appearing of microbubles into the renal parenchyma extending from the base of calices demonstrates intrarenal reflux. It is observed mainly in young infants with high grade reflux, indicating those who have higher risk for renal infection and scaring and thus need more careful follow-up (Figure 2).

In comparison with VCUG ceVUS has superior sensitivity for detecting VUR ranging from 80-100%, and specifity from 85-100% [19-23]. From clinical point of view it is important that the refluxes missed by VCUG were predominantly of higher grade, than those missed by ceVUS [19,21-22]. There are few pathophysiological mechanisms that can explain these phenomena: VUR has intermittent character and may varies in appearance and grade, sometimes even during the same investigation; radiographic contrast could be markedly diluted in dilated system present in high grade reflux; to escape unnecessary radiation fluoroscopic time during VCUG might be quite short and insufficient to depict reflux [1,19]. In contrast, observation time in ceVUS is longer allowing depicting even intermittent refux and especially high grade refluxes. On the other side ceVUS can miss low-grade refluxes because of difficulty in visualizing retrovesical regions by this method. However, it is known that usually grade I reflux on VCUG appears as grade I-II reflux on ce-VUS due to its higher sensitivity to depict even a few refluxing microbubbles which easily move up from the ureter to the renal pelvis. So, the risk of missing grade I reflux on VUS is almost minimal. The clinical significance if such refluxes is questionable [1,19].

Initially, ceVUS has been used mainly to study VUR. Lately it has been demonstrated that ceVUS has ability to depict structure of the urethra in both sexes [42,43], something that was previously possible only by using VCUG. It has been shown that by using ceVUS diagnosis of posterior urethral valves and other most prevalent urethral pathology can be done [13,43].

In our study, the urethra was visualized in majority of patients (76%), except in those who refused to void. We did not found any significant urethral pathology, except "*spinning top urethra*" revealed in 9 girls (Figure 1). Spining top urethra can be a part of physiological spectrum but it can also indicate functional bladder problem, especially if clinical symptoms of dysfunction are present. Thus this finding can help clinicians to design adequately further urological workout. Urodynamics performed in 5 of our patients with spinning top urethra documented bladder dysfunction.

CeVUS requires catheterization of the urinary bladder thus takes risk of iatrogenic UTI. However, catheterization is unavoidable in any type of cystography, e.g.VCUG, radionuclide cystography (RNC) or voiding urosonography respectively. It is stressful at least to some patients and parents. Our observation is that small babies accept

catheterization much easier than older, indicating that the catheterization itself is not painful. In comparison with VCUG the examination is in a childfriendlier environment with the parents close to the child, and allowing the child to void during ceVUS in more physiologic positions. Additional advantage is that there is no risk of adverse reactions associated with administration of iodine contrast. Ability to store films of the examinations on the hard drive enables consultations with other specialists if necessary and may be used for didactice purposes.

The limitations of ceVUS include the longer duration of examination compared to VCUG; the need to directly engage a radiologist; dependence on the examiner's experience and higher cost of contrast agent in comparison with iodine agents.

Currently, ceVUS is starting to be used not only as alternative method to VCUG but as an imaging method of choice for diagnosis of VUR and other most prevalent urethral pathology (Figures 4, 5 and 6), regardless of age and sex [13,24-25,44]. Radiation associated VCUG should be reserved only for limited number of patients with complex anomalies of distal urinary tract requiring detailed anatomical assessment.

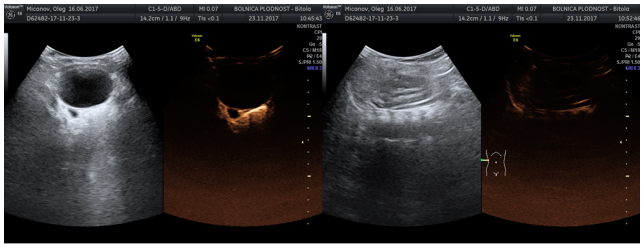

Figure 4: Hydroureter without Reflux.

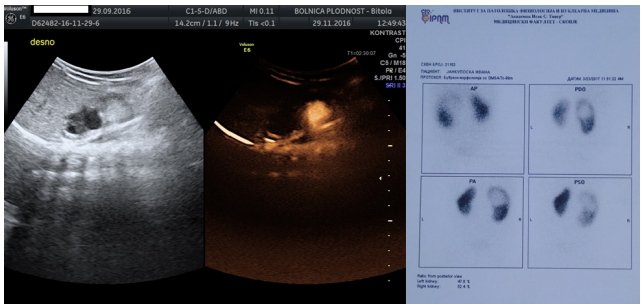

Figure 5: VUR into the Lower Pole of Duplex Collecting System shown by ceVUS - Afunctional obstructed right upper pole on DMSA scan.

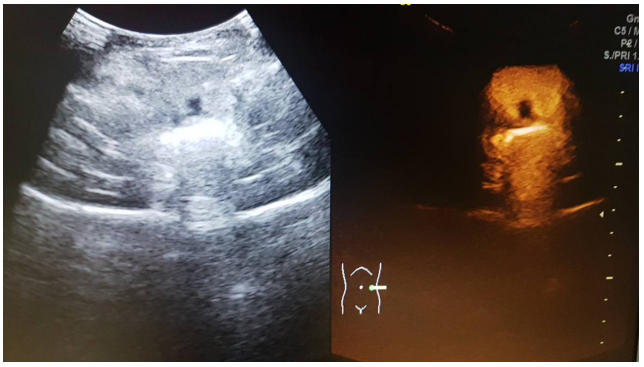

Figure 6: Ureterocela corresponding to the obstructed upper pole of duplicated collecting system shown by ceVUS.

Conclusion

Radiation exposures as low as reasonably achievable continue be a concern in imaging of pediatric patients. CeVUS as radiation free method with diagnostic performance comparable to VCUG respectively is in line with this principle. In our experience ceVUS allows detection and grading of VUR and diagnosis of most prevalent pathology of the distal urinary tract and urethra.

In our opinion ceVUS should be incorporated into imaging protocols for management of pediatric UTI and antenatal hydronephrosis instead of radiation associated VCUG in most clinical instances.

Conflict of Interest

The authors declare no conflicts of interest.

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