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The role of ultrasound in the diagnosis of vesicoureteral reflux disease

Gulec Mert Dogan [1], Ahmet Sığırcı [1], Ahmet Taner Elmas [2], Yilmaz Tabel [2]

[1] Department of Pediatric Radiology, Inonu University, Malatya, Turkey
[2] Department of Pediatric Nephrology, Inonu University, Malatya, Turkey

ORCID ID of the author(s)

GMD: 0000-0002-2305-9625
AS: 0000-0001-9221-0002
ATE: 0000-0002-9749-6115
YT: 0000-0001-7359-4944

Corresponding Author
Gulec Mert Dogan
Inonu University, Department of Pediatric Radiology, Malatya, Turkey
E-mail: dr_gulecmert@hotmail.com

Ethics Committee Approval
The study was approved by the local Ethics Committee of University of Health Sciences, Inonu University (approval number: 2021/1807, data: 23.03.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The gold standard in the diagnosis of VUR (vesicoureteral reflux) is voiding cystouretrography (VCUG), but it is an invasive test with risk of radiation. The aim of the study was to determine the sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) of ultrasound (US) in the diagnosis of VUR.

Methods: 760 kidneys of 380 patients were examined in this cohort study. The patients were grouped by three age groups; 0-2, 3-5 and 6-17 years old. US reports included the data of anteroposterior renal pelvic diameter (APRPD), kidney parenchyma, kidney size, and the size of ureters. For all age groups, the sensitivity, specificity, PPV and NPV were evaluated separately in two circumstances; APRPD is accepted pathologic when >5 mm and >10 mm.

Results: A correlation was found between VCUG and US results in all age groups (P<0.001). When pathologic APRPD was accepted as >5 mm, sensitivity, specifity and NPV of US were 86.99%, 60.26% and 88.13% respectively, regardless of age. In contrast, when pathologic APRPD was >10 mm, sensitivity, specifity and NPV were 79.45%, 79.91% and 71.17%, respectively. Sensitivity and NPV of US were found highest in group of 0-2 age.

Conclusion: If US are performed by radiologists experienced in the pediatric urinary system US and if it includes other parameters with APRPD, it will guide for VCUG in the diagnosis of VUR. Thus, radiation exposure can be minimalized in clinical practice.

Keywords: Ultrasonography, Voiding cystourethrography, Vesicoureteral reflux

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Introduction

The vesicoureteral reflux (VUR) disease is present in the etiology of urinary tract infections in children with a rate of 30-40% [1]. VUR is also responsible for 25% of end-stage renal disease [2]. In 90% of VUR in pediatric patients, there is a congenital problem in the vesicoureteral junction [2]. The gold standard in the diagnosis of VUR is voiding cystouretrography (VCUG), which is an invasive diagnostic test with a risk of radiation exposure. The children are more sensitive to radiation, and the application of VCUG is difficult for children. Therefore, application of VCUG examination should be meticulously decided for children with accurate indications. In the last guideline, VCUG is not recommended in children < 2 years of age, if the ultrasound is normal in the first urinary tract infection [3]. This has increased the importance of ultrasound (US) for the decision of VCUG indication. US is noninvasive, radiationless, and easy to apply.

Urinary tract dilatation (UTD) is one of the most common indications of VCUG in children, as well as recurrent urinary tract infections. Various classification systems have been developed to categorize UTDs [4, 5]. In these multiparametric systems, anteroposterior renal pelvic diameter (APRPD) is also used as a quantitative value. However, a consensus cannot be established within definitions of different threshold values for APRPD.

The aim of the study was to determine the sensitivity, specificity, positive and negative predictive values (PPV and NPV) of US in the diagnosis of VUR and to determine the role of US in performing VCUG with absolute indications. In addition, we aimed to show the effect of differentiation in pathologically accepted APRPD values on the sensitivity, specificity, PPD and NPV of US examinations done for detection of VUR.

Materials and methods

All procedures were followed in accordance with the Helsinki Declaration, all parents of patients have been informed and have been approved to participate in this study. This study was approved by the Inonu University Ethical Committee with number 2021/1807 at 23-03-2021.

Patients between ages of 0-17, who were referred to our department from the pediatric nephrology department for VCUG imaging due to urinary tract infection and hydronephrosis between January 1, 2017 and December 31, 2017 were included in our study.

Children with a history of neurogenic bladder, congenital and acquired urogenital anomalies were excluded from the study. All VCUGs and USs were analyzed retrospectively through the PACS system of our hospital. A total 760 kidneys of 380 patients were evaluated in our study. The patients were grouped by three, according to their ages. Group 1, 2 and 3 includes patients with ages 0-2, 3-5, and >5, respectively.

US findings

US of all patients were performed by the same pediatric radiologist, who had 2 years experience in pediatric radiology with GE LOGIC S8, USA. All USs were performed at least one week before VCUG. For the evaluation of hydronephrosis, SFU classification system was used in our department in 2017 [6]. In addition, all US reports written by the pediatric radiologist included findings related to the kidney parenchyma, kidney size, and the size of ureters (Figure 1). Children, whose US examinations are not performed by a pediatric radiologist or US reports contain missing information, were excluded from the study. Pathologies in US reports were also grouped in 3 among themselves. Patients with pathological APRPD were in group 1, patients with small kidney size, increased renal parenchyma echogenicity, increased ureter diameters, thick ureter wall were classified as group 2, patients with pathological APRPD and small kidney size, increased renal parenchyma echogenicity, increased ureter diameters, thick ureter wall were classified as group 3. Hydronephrosis and prominent renal pelvis were defined by APRPD ≥10 mm and ≥ 5 mm in the supine position, respectively [7].

VCUG findings

Reflux evaluation was done by 2 pediatric radiologists, A.S had 12 years and G.M.D. had 2 years experience in pediatric radiology. VUR was classified 0 to 5 according to the International Reflux Study Classification [8]. Grade 1, 2, and 3 VUR were accepted as low-grade reflux (Figure 2), whereas Grade 4 and 5 VUR were accepted as high-grade reflux.

Sensitivity, specificity, PPV and NPV of US were calculated for reflux detection, by comparing VCUG as a reference method.

Figure 1: Imaging in the sagittal plane US. The parenchyma of the left kidney was abnormal, but APRPD was normal.

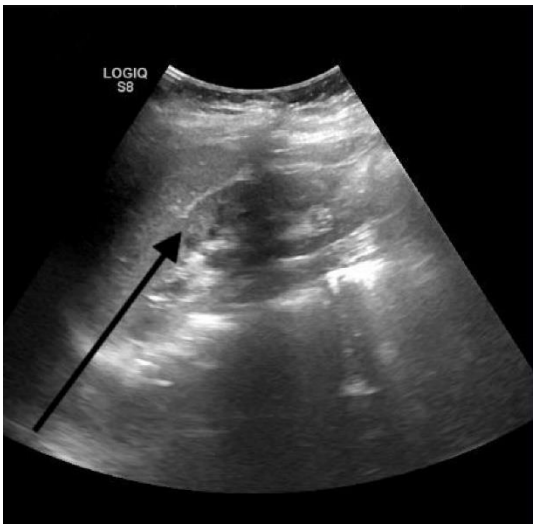


Figure 2: VCUG. There was a grade 3 reflux (low-grade reflux) to the left kidney.

Statistical analysis

SPSS version 22 (IBM, Armonk, NY, United States) was used to evaluate the data. Categorical data were expressed as count and percentage. Pearson's chi-square test and ROC analysis were used for comparisons based on independent groups. Sensitivity and specificity comparisons were performed by McNemar test. *P*-values <0.05 were considered statistically significant.

Results

The male and female ratios in our study were 53.4% (n=203) and 46.6% (n=177), respectively. 33.5% (n=127) of patients were 0-2 years old, 25.5% (n=97) were 3-5 years old, whereas 41% (n=156) were 6-17 ages, and the average was 5.8.

Reflux was observed in 216 (28.4%) of 760 kidneys with VCUG . While 98 (45.3%) of these were high grade, 118 (54.7%) were low grade. If APRPD >5mm was considered as pathological, 57.9% (n=122) of urinary USs were pathological. Of these 122 US examinations, 93 (42.2%) did not show reflux on VCUG (false positive), and the pathology was related to APRPD in 67 (72%). Among the pathologies causing false positivity, the number of those related to APRPD was statistically significantly higher than the other groups (P<0.001).

If APRPD >10 mm (hydronephrosis) was considered as pathologic; 44.8% (n=170) of urinary USs were pathological. 44 (25.8%) USs were pathological without reflux on VCUG (false positive). The pathology was related to APRPD in 26 (59%) of these USs. Among the pathologies that cause false positivity, the number of those related to the APRPD was higher than the other groups, but it was not statistically significant (P=0.08).

Aside from VCUG being the gold standard, sensitivity, specificity, PPV and NPV of US, AUC (area under the curve) and *P*-values according to age ranges were given in detail in Tables 1 and 2 (Figure 3, 4). A correlation was found between VCUG and US results in all age groups (P<0.001).

Table 1: Results of the ROC analysis for APRD >10 mm

Age	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*-value	AUC
0-17	79.45	79.91	71.17	86.18	<0.001	0.797
0-2	84.78	69.14	60.94	88.89	<0.001	0.770
3-5	82.86	83.87	74.36	89.66	<0.001	0.834
>5	73.85	86.81	80.00	82.29	<0.001	0.803

APRPD: anteroposterior renal pelvic diameter. PPV: positive predictive values, NPV: negative predictive values VCUG: voiding cystouretrography, AUC: Area under curve. The results APRPD >10mm in determination of the necessity of VCUG is summarized.

Figure 3: ROC curve for APRPD >10 mm for determination of the indication of VCUG

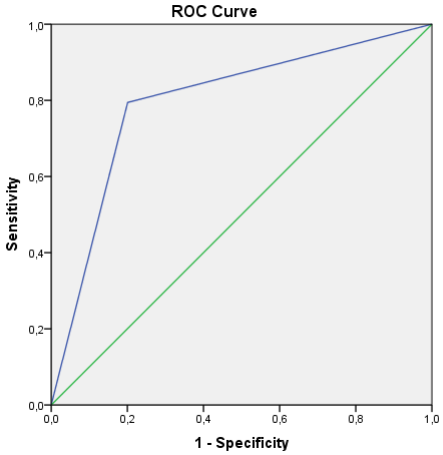
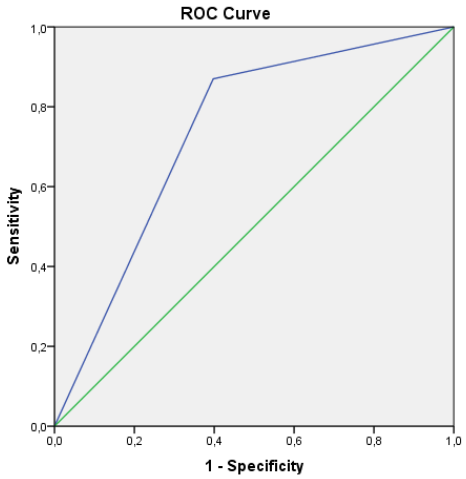


Table 2: Results of the ROC analysis for APRD >5 mm

Age	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*-value	AUC
0-17	86.99	60.26	57.73	88.13	<0.001	0.736
0-2	95.65	37.04	46.32	93.75	0.002	0.663
3-5	88.57	72.58	64.58	91.84	<0.001	0.806
>5	80	72.53	67.53	83.54	<0.001	0.763

APRPD: anteroposterior renal pelvic diameter. PPV: positive predictive values, NPV: negative predictive values VCUG: voiding cystouretrography, AUC: Area under curve. The results APRPD >5 mm in determination of the necessity of VCUG is summarized.

Figure 4: ROC curve for APRPD >5mm for determination of the indication of VCUG



Discussion

VUR is an important health problem that is seen in 0.5-1.5% of the children [9]. High-grade VUR is more likely to develop injuries in kidney. Therefore, antibiotic prophylaxis is not recommended in patients with low-grade VUR in the last guidelines, although these children need antibiotic prophylaxis and / or surgical treatment [10]. VCUG, which is used for diagnosis of VUR as the gold standard, is not an appropriate diagnostic method in the screening and follow-up of patients due to its high radiation risk and being invasive [9]. US is a non-invasive examination that is easy to perform and has no radiation, and it is used as a screening method in many centers, especially in the follow-up of urinary tract infection and hydronephrosis. US is recommended by the American Academy of Pediatrics (AAP) as a screening method for predicting the presence of VUR in patients with urinary tract infections [3].

In our study, the sensitivity and NPV of US for reflux were found to be 79.45% and 86.18%, respectively. In the literature, the sensitivity and NPV of US is reported in a wide range between 16-40% and 25-86% for VUR [11], respectively. Preda et al. [12] reported the sensitivity of US for reflux to be %63, whereas Massanyi et al. [11] reported 42% and 86% for low and high grade reflux, respectively. There were 98 kidneys with high grade reflux in our study cohort and only 6 (6.1%) of these kidneys were not pathological in US. This supports that US can be a guide for VCUG examination. In previous studies, the number of patients with high grade reflux were quite low compared to our numbers [13-15]. Our study group included patients of a university hospital with pediatric surgery, a pediatric radiology, and a pediatric nephrology departments, where complicated cases were referred from other hospitals. That revealed the difference in our patient population.

Although there are studies favoring US [15], there are also studies emphasizing the possibility of diagnostic delay of grade 4-5 reflux with a normal US which points out not to use US as a screening test for VUR [13]. Just like Massanyi et al. [11],

Nelson et al. [16] claims that US cannot be used as a screening test for VUR alone due to its low sensitivity and NPV. Compared to the literature, our results were better explained. We expressed the reasons for these results; all of US examinations were performed by the same pediatric radiologist in the study, the status of bladder and ureters, kidney size, and parenchymal features were described in detail in our reports, and non-detailed US examinations were excluded from the study. In most of the previous studies, none of these parameters were not evaluated in US [13, 17, 18]. In some studies emphasizing the importance of US parameters other than APRPD (such as decreased renal size, increased renal parenchymal echogenicity and ureteral dilation), decreased renal size and ureter dilatation were found to be the most important parameters [19, 20].

Most of the studies for US sensitivity for VUR are reported in 0-2 age group in the literature. There are only a few studies comparing the sensitivity of different age groups [21, 22]. Otukesh et al. [21] compared colored doppler voiding urosonography with radionuclide voiding cystography, found that US of young children were more sensitive for reflux, and claimed that the reason for this was the increased sonographic resolution in young children. Ilikan et al. [22] showed a correlation between US and VCUG results in the 0-6 age group, while no correlation was found for >6 years old. In this study, sensitivity and NPV for 0-6 years were 89.76% and 81.2%, whereas for >6 years, sensitivity and NPV were 50.49% and 65.8%, respectively [22]. US results were consistent with VCUG results across all age groups in our study, while 0-2 age group had the highest sensitivity and NPV (84.78% and 88.89%, respectively).

On the other hand, Ilikan et al. [22] found the specificity lower in the 0-6 age group than in the >6 age group. Despite the high sensitivity and NPV in the 0-2 age group, the specificity was as low as 37.04% in our study. The lowest specifity between the groups in our study was in the 0-2 age group, whereas 0-6 age group in the study of Ilikan et al. [22].

The screening with US should reduce the risk of excessive radiation exposure with VCUG imaging as much as possible. When US reports with APRPD >10 mm are considered as pathological, the specificity was 79.91% for all age groups and 69.14% for 0-2 age group. Also, the sensitivity and NPV were still quite high when compared with the literature. In addition, the number of kidneys that caused false positive decreased from 93 to 44. US results causing false positive were clearly related to pathologically accepted APRPD value. In the last guidelines, APRPD 10 mm and above, together with other parameters, was considered pathological [4]. Excessive false positives and low specificity in the 0-2 age group were an expected result depending on the APRPD. One of the most common reasons for performing urinary US in radiology departments for 0-2 age group is the follow-up of hydronephrosis detected in the antenatal period. Most of the dilatations in the pelvicalyceal system are transient in these patients. If there are not any additional findings such as ureter dilatation, and calyceal, parenchymal or clinically severe urinary tract anomaly, surgical treatment is less required in patients with APRPD <10 mm [23]. Also prominent renal pelvis can be detected incidentally in children and it is not related to VUR [24].

Limitations

The most important limitation of our study was being retrospective. Secondly, US is a method that gives subjective, user-dependent results.

Conclusion

We agree with the recent trend in reducing radiation exposure in the radiology community. If US is performed by an experienced radiologist and includes other parameters with APRPD, it will guide for the indication of VCUG in the diagnosis of VUR. By that, some children can be saved from unnecessary radiation exposure.

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