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Is There Any Difference in the Predictive Findings for VUR in Different Age Groups? Evaluation of VCUG and USG Examinations in 539 Children with Febrile Urinary Tract Infection

Farklı Yaş Gruplarında VUR için Prediktif Bulgularda Fark Var Mıdır? Ateşli İdrar Yolu Enfeksiyonu Olan 539 Çocuğun USG ve VCUG Muayenelerinin Değerlendirilmesi

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ABSTRACT

Background: The clinical presentation and the course of vesicoureteral reflux (VUR) vary according to age. All guidelines for the evaluation of urinary tract infections (UTIs) focus on infants under 2 years of age. To determine which factors might predict the presence of VUR among different age groups, we retrospectively reviewed the factors including patient characteristics and renal bladder ultrasonography (RBUS) and findings obtained from voiding cystourethrography (VCUG) examinations in a children's hospital.

Materials and Methods: RBUS and VCUG reports of 539 patients performed for febrile UTI in 2016 were reviewed. The associations between RBUS findings and abnormalities found in VCUG findings were investigated. The predictive findings of RBUS for VUR were evaluated among three age groups (0-2 y, 2-5y, and >5 years).

Results: In total, 368 girls (68.3%) and 171 boys (31.7%) with a mean age of 6.29+4.18 years were evaluated. RBUS results were abnormal in 78.5% of patients. VUR was reported in 284 (52.7%) patients who underwent a VCUG. A significant result in the multivariate analysis of patients at 0-2 years of age was that RBUS renal parenchymal thinning was a predictor of VUR. Patients over 5 years of age were found to have a higher risk of VUR when patients had moderate to severe hydronephrosis accompanying parenchymal thinning.

Conclusion: In children younger than 2 years, thinned parenchymal thickness helped predict the findings for VUR. Predicting the presence of VUR made no significant difference among the RBUS findings in children at the age of 2-5 years. Thinned parenchymal and moderate to severe hydronephrosis were significantly correlated with the presence of reflux for children older than 5 years.

Keywords: Vesicoureteral reflux, renal bladder ultrasonography, voiding cystourethrography

ÖZ

Amaç: Vezikoüreteral reflünün (VUR) klinik prezentasyonu ve seyri yaşa göre değişim göstermektedir. İdrar yolu enfeksiyonlarının (İYE) değerlendirilmesi için yapılmış tüm kılavuzlar 2 yaş altındaki çocuklar üzerinde yoğunlaşmaktadır. Değişik yaş grupları arasında VUR düşündürecek faktörleri tespit etmek amacıyla bir çocuk hastanesindeki hasta özellikleri, üriner ultrason (RBUS) ve voiding sistoürerografi (VCUG) bulguları dahil olmak üzere retrospektif olarak değerlendirildi.

Gereç ve Yöntemler: 2016'da ateşli İYE nedeniyle 539 hastaya yapılmış olan RBUS ve VCUG raporları değerlendirildi. RBUS bulguları ve anormal VCUG bulguları arasındaki ilişki araştırıldı. RBUS'de görülen, VUR düşündürecek bulgular üç yaş grubu arasında değerlendirildi (0-2 yaş, 2-5 yaş, ve >5 yaş).

Bulgular: Ortalama yaşı 6,29+4,18 yıl olan toplamda 386 kız ve 171 erkek değerlendirildi. Sıfır-iki yaş arası hastalarda yapılan çok değişkenli analizde, RBUS'de böbrekte parankimal incelme görülmesi VUR açısından anlamlı olarak sonuçlandı. Orta-ileri derece hidronefroza eşlik eden parankimal incelmesi olan 5 yaş ve üzeri hastalarda VUR riskinin daha yüksek olduğu görüldü.

Sonuç: Parankim kalınlığının incelmesi 2 yaş altındaki hastalarda VUR düşünülmesinde yardımcı olmuştur. İki-beş yaş arası çocuklarda VUR düşünülmesi RBUS bulguları arasında anlamlı değişiklik oluşturmamıştır. Beş yaştan büyük çocuklarda VUR varlığı ile incelmiş parankim ve orta-ileri derece hidronefroz varlığı arasında anlamlı ilişki olduğu görülmüştür.

Anahtar Kelimeler: Vezikoüreteral reflü, üriner sistem ultrason, voiding sistoüretrografi

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Introduction

Vesicoureteral reflux (VUR) is a common condition in children. The incidence of VUR is 0.4-1.8% in children and 25-40% of those children have acute pyelonephritis (1,2,3,4). Voiding cystourethrography (VCUG), the most common fluoroscopic study method used for children, is the gold standard for the diagnosis of VUR (5,6). VCUG is an invasive procedure that carries the risk of radiation exposure and iatrogenic urinary tract infections (UTI), and requires urethral catheterization, which can be stressful for children and their families (7,8,9). Therefore, the indication must be evaluated very carefully.

There is no consensus on imaging studies to be performed on a child with febrile UTI in different guidelines (10). The European Society of Pediatric Urology (ESPU) guidelines recommended renal and bladder ultrasonography (RBUS) in all children with febrile UTIs (11). VCUG or dimercaptosuccinic acid (DMSA) scanning (the bottom-up or the top-down approach) is advised in all patients with febrile UTI and aged <1 year. The American Academy of Pediatrics (AAP) guidelines (12) recommend children between the ages of 2 and 24 months who present an initial febrile UTI should have an RBUS. Only if there are abnormalities on the RBUS or after a second febrile UTI, patients should be considered for a VCUG.

The clinical presentation and course of VUR vary by age. A biphasic age distribution occurs when children are diagnosed with VUR based on their presentation. The first group is recognized following an investigation of antenatal hydronephrosis, predominantly in males. The second group is diagnosed later, after a UTI, and is predominantly female (13,14). In guidelines, when and how to investigate the presence of VUR in children with a febrile UTI is defined depending on the age and gender of the patient (10,11,12). However, there are no studies evaluating whether diagnostic RBUS and VCUG investigations differ according to age group in the literature. The aim of this study was to investigate whether US and VCUG examinations of different age groups differed in revealing the presence of VUR.

Material and Methods

Permission from the Ethics Committee (number 2018-128) was obtained from the Ankara City Hospital, Child Health and Diseases, Hematology and Oncology Training and Research Hospital. We retrospectively evaluated the medical records of 539 children who underwent VCUG and RBUS investigation for febrile UTI between January 1, 2016, and December 31, 2016. Consent form was obtained from the patients' families. The VCUG and RBUS reports were received from hospital records. VCUG and RBUS that were performed for other indications such as antenatal hydronephrosis, neurogenic bladder etc. were not included.

The cases in all age groups with febrile UTI in our hospital were investigated with RBUS. We included children with confirmed febrile UTIs, with positive urinalysis and culture results. The cases with recurrent UTIs and first febrile UTI cases with RBUS findings including hydronephrosis, ureter dilation, increased parenchymal echogenicity, and decreased parenchymal thickness underwent VCUG evaluation. Children with a single UTI did not undergo VCUG if they had a normal RBUS.

The UTI was considered certain if there was any growth of a single uropathogen in a suprapubic aspiration or if there was the growth of a single uropathogen in 100,000 colony-forming units per milliliter (CFU/mL) in one or more samples of clean-catch urine or bag specimen with urinalysis results consistent with UTI (positive leukocyte esterase test, nitrite test, or microscopic analysis positive for leukocytes or bacteria). The term "febrile" was determined to be 38.0 °C. The criteria for "recurrent UTI" were fulfilled if the child had another culture-confirmed UTI between the first febrile UTI and the VCUG.

The RBUS was performed at the time of diagnosis of UTI, while VCUG was performed 4 weeks after the infection resolved.

The RBUS findings included hydronephrosis, ureter dilation, parenchymal echogenicity, and parenchymal thickness. In this study, echogenicity of kidney was classified as either normal or increased. Dilation was graded based on the report provided by the radiologist staff on duty; grades expressed the Society for Fetal Urology scale (15). Ureter morphology was categorized as "dilated" or "not dilated" without diameter data.

The diagnosis and grade of VUR was identified through VCUG on the basis of international reflux classification (16). Children with grade 1 to 3 reflux were stratified as having low-grade reflux, while those with grade 4 to 5 reflux as having high-grade reflux.

Patients were divided into three groups according to ages (0-2 years; 2-5 years; >5 years). Predictive findings detected in RBUS for VCUG indication were compared in different age groups.

Statistical Analysis

Descriptive continuous variables were presented as mean, standard deviation, and minimum and maximum values, and categorical values were defined as percentages. Continuous variables from the two groups were compared using the Mann-Whitney U test, and groups of more than two were compared using the Kruskal-Wallis variance

analysis. Nominal variables of two or more groups were compared using either the chi-square test or the Fisher's Exact test. RBUS performance on VUR diagnosis was tested using diagnostic accuracy criterion (sensitivity, specificity, positive predictive value, and negative predictive value). We analyzed the relationship between ultrasonography and cystourethrography using generalized estimating equations to take into account that the two kidneys from the same patient could not be considered independent. This method is seen as an extension of the general linear models developed for the dependent data. In this method, general linear models are adapted to the marginal distributions of repetitive dependent variables. Statistical analyses were performed using SPSS, version 12.0 of the program (Chicago Inc., 2006), and $p<0.05$ was accepted as significant.

Results

In our children hospital, 671 VCUG examinations were performed in 2016. The indications for VCUG were febrile UTI (n=539, 80.3%), neurogenic conditions (n=50, 7.5%), antenatal hydronephrosis (n=36, 5.4%), voiding disorders (n=33, 4.9%), and others (trauma-anotomic abnormalities) (n=13, 1.9%).

Patient Characteristics

Only cases with febrile UTI were included in the study. There were 368 females (68.3%) and 171 males (31.7%), totally 539 cases with a mean age of 6.29±4.18 years (range: 0.08-18 years). Thirty-six of the cases also have a diagnosis of antenatal hydronephrosis in addition to UTI. group 1 consisted of 124 infants aged <2 years (23%); group 2 consisted of 122 children aged 2 to 5 years (22.6%); and group 3 consisted of 293 children older than 5 years (54.4%). The ratio of female patients was significantly higher in the group of children older than 5 years compared to the other age groups (74.1% in the group of children older than 5 years old, 60.6% in the group of children aged 2-5 years, and 62.1% in the group of children younger than 2 years, $p<0.001$). Demographics and imaging results are shown in Table 1.

Abnormalities such as hydronephrosis, ureter dilation, parenchymal dilation, parenchymal thinning, or increased echogenicity were noted in 423 (78.5%) cases on RBUS. One hundred sixteen (21.5%) of patients had entirely normal RBUS findings. Pathological bladder findings were detected in 167 patients (30.9%). VCUG was performed to patients who had abnormal findings in the RBUS in the first febrile urinary tract infection, or who had normal RBUS and recurrent febrile urinary tract. VCUG findings were pathologic in 284 (52.7%) patients and normal in 255 (47.3%) patients.

Table 1. Patients demographics and imaging findings in 539 cases

Gender male female total 0-2 years 47 (37.9%) 77 (62.1%) 124; 23% 2-5 years 48 (39.4%) 74 (60.6%) 122; 22.6% > 5years 76 (25.9%) 217 (74.1%) 293; 54.4% Total 171 (31.7%) 368 (68.3%) 539; 100%		
Findings of ultrasonography investigation		
Ultrasonography findings	**n**	**%**
Normal (recurrent fUTI)	116	21.5
Abnormal (first fUTI)	423	78.5
Total	539	100
VCUG findings	**n**	**%**
VUR		
No	255	47.3
Yes	284	52.7
Laterization of VUR		
Right	84	29.6
Left	89	31.3
Bilateral	111	39.1
Total	284	100
VUR grades		
Grade 1	34	11.9
Grade 2	60	21.1
Grade 3	97	34.2
Grade 4	63	22.2
Grade 5	30	10.6

fUTI: Febrile urinary tract infection, VCUG: Voiding cystourethrogram, VUR: Vesicoureteral reflux, p-value <0.05

Factors That Indicate the Existence of VUR

The sensitivity and specificity of the RBUS to identify VUR were 80.2% and 24.4%, respectively. False positivity [95% confidence interval (CI)] was 54.5%, and the false negative rate (95% CI) was 52.4%. Univariate analysis results comparing the non-refluxing group with the refluxing group are listed in Table 2. Age and gender had no significant effect on VUR. The refluxing group had significantly higher numbers of patients with hyronephrosis, thinned parenchyma, and increased echogenicity.

The results of univariate and multivariate analyses, designed with a generalized linear model distinguishing the non-refluxing group from the refluxing group for all three age groups, are shown in Tables 3 and 4. In children younger than 2 years, a significant variable which predicted the presence of reflux was thinned parenchyma. No significant difference in predicting the presence of reflux was found among the RBUS findings in children aged 2-5 years. Thinned parenchyma and moderate to severe hydronephrosis were significantly correlated with the presence of reflux for the children older than 5 years.

Table 2. Statistical analysis results between the non- refluxing and refluxing groups

Variables	VUR (-)		VUR (+)		
	N, (M/F)	%	N, (M/F)	%	p
Age groups					
Younger than 2 years	59 (M26/F33)	46.7	65 (M21/F44)	53.3	0.654
2-5 years	50 (M14/F36)	34.6	72 (M34/F38)	65.4	
Older than 5 years	147 (M31/F116)	29.4	156 (M45/F111)	70.6	
Hydronephrosis					
No	97	34.5	184	65.5	**0.044**
Mild	66	41.7	92	58.3	
Moderate-severe	21	21	79	79	
Parenchyma					
Normal	145	39.8	219	60.2	**0.000**
Thinned	39	22.3	136	77.7	
Ureter					
Not dilated	154	35.1	284	64.9	0.235
Dilated	30	29.7	71	70.3	
Echogenicity					
Normal	145	36.1	257	63.9	**0.004**
Increased	39	28.5	98	71.5	

VUR: Vesicoureteral reflux, p-value <0.05, N: Number of patient, M: Male, F: Female

Table 3. Generalized estimating equations analysis results of age groups for the prediction of VUR

p		<2 years		2-5 years		>5 years	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	
Gender	Female Male	0.053	1.756 (0.992- 3.109)	0.415	0.789 (0.447- 1.394)	0.215	0.779 (0.524- 1.157)
Hydronephrosis	No Mild Moderate- severe	0.067	0.552 (0.292- 1.043)	0.661	0.824 (0.346- 1.960)	**0.008**	0.488 (0.287- 0.831)
Parenchymal thickness	Normal Thinned	**0.003**	0.481 (0.296- 0.784)	0.237	0.700 (0.387- 1.265)	**0.004**	0.583 (0.403- 0.844)
Ureter	Not dilated Dilated	0.155	0.603 (0.300- 1.212)	0.181	0.557 (0.236- 1.313)	0.795	0.924 (0.509- 1.677)
Parenchymal Echogenicity	Normal Increased	0.355	0.549 (0.154- 1.958)	0.111	0.381 (0.116- 1.247)	0.375	0.663 (0.268- 1.643)

VUR: Vesicoureteral reflux, p-value <0.05, OR: Odds ratio, CI: Confidence interval

In cases with increased renal echogenicity, it was observed that the likelihood of VUR increased significantly. In patients under 2 years of age, the RBUS examination revealed that those who had renal parenchymal thinning were twice as likely to have VUR. In patients over 5 years of age, the risk of VUR was 2.27 times higher in patients with moderate and severe hydronephrosis than in patients without hydronephrosis. In patients with parenchymal thinning, the risk of VUR was 2.7 times higher than those without thinning.

Table 4. Predictors of VUR based on RBUS for age groups

Age groups	Parameter	p	Odds ratio	95% CI
0-2	Parenchymal thickness, normal	0.029	0.498	0.266- 0.931
Over 5 years	Parenchymal thickness, normal	0.029	0.63	0.415- 0.954
	No hyrdonephrosis	0.048	0.557	0.312- 0.994

VUR: Vesicoureteral reflux, p-value <0.05, CI: Confidence interval

It was noted that the presence of antenatal diagnosis (p=0,041) and the increase in bladder wall thickness (p=0.032) in RBUS were significant findings for VUR. It was observed that antenatal diagnosis alone increased the probability of VUR 2.2 times, and elevated bladder wall thickness increased the probability of VUR 1.51 times.

The incidence of high grade (grade 4-5) VUR was significantly correlated with the presence of hydronephrosis [Odds ratio (OR)=1.44, 95% CI (1.04-2.0), p=0.027], decreased parenchymal thinning [OR=1.487,95% CI (1.14-1.92), p=0.003], ureteral dilatation [OR=1.58, 95% CI (1.07-2.339, p=0.02], and an increased grade of parenchymal echogenicity [OR=1.89,95% CI (1.10-3.24), p=0.02].

No statistically significant difference was found between the patients who had a first febrile urinary tract infection and those who had recurrent febrile ITUs in terms of age, gender and the presence of VUR (Table 5).

Discussion

There is a controversy on the precise indications for VCUG after a first febrile UTI. Children under two years of age were carefully evaluated for UTIs, especially since their symptoms were not specific and the chances of renal damage were high. All guidelines provide recommendations on how to evaluate UTIs, especially in children under 2 years of age (10). The AAP (12) guidelines recommend VCUG after abnormal renal ultrasound or 2 febrile urinary tract infections. The ESPU guidelines (11) advise VCUG or DMSA for all children with UTI. With new advancement in fluoroscopy, the radiation exposure with variable rate pulsatile fluoroscopy is reported 10 times less than that of the traditional continuous fluoroscopic units and 5 times less than that of a DMSA scan (17). Because anatomical details can be seen better and VUR grading can be done in our hospital, VCUG evaluation is preferred to DMSA after RBUS investigation. The study presents data to determine which factors might predict the presence of VUR among three age groups (0-2 y, 2-5 y, and >5 years). In our study, according to the evaluations, observing thinned parenchyma in children under the age of 2 years and over 5 years was predictive of VUR. RBUS examination is not a predictor in patients aged 2-5 years; therefore, the evaluation of patients aged 2-5 years must be performed more carefully.

In the evaluation of VUR in children, significant attention has been given to the assessment of hydronephrosis shown with RBUS and cortical scars shown with renal scintigraphy. There is no information about predictive findings for VUR on USG for different age groups in the literature. Although patients with normal RBUS may have a high-grade VUR, a significant correlation between the severity of hydronephrosis and reflux grade has been shown before (18). In our study, the frequency of VUR increased significantly in patients with moderate to severe hydronephrosis. However, little attention has been given to renal parenchymal thickness or echogenicity detected through RBUS. Renal parenchymal thinning was another predictive factor for the risk of VUR in patients. In the children older than five years, who were investigated due to a UTI, because of the late presentation of reflux nephropathy, the presence of hydronephrosis and parenchymal thinning detected on ultrasonography significantly increased the risk of VUR. Although increased renal parenchymal echogenicity is a common renal ultrasonography finding in patients with recurrent UTI (19) and first febrile UTI (20), echogenicity of the kidney is not noted as a predictive factor for VUR in children in other studies. Our findings on echogenicity of the kidney is contributed as a new scientific finding on this issue.

The predictors of high-grade VUR detected on RBUS included dilated ureter, moderate to severe hydronephrosis, parenchymal thinning, and increased echogenicity.

Table 5. Number of patients per group, age, sex, the absence or presence of VUR and first febrile UTI or recurrent febrile UTI

VUR +		Male		Female		Total
		VUR +	VUR -	VUR +	VUR -	
First febrile UTI	0-2 years	18 45%	22 55%	36 59%	25 41%	101 23.9%
	2-5 years	29 69%	13 31%	28 50%	28 50%	98 23.2%
	<5 years	36 57%	27 43%	79 49%	82 51%	224 52.9%
	Total	83 57%	62 43%	143 51%	135 49%	423 79%
Recurrent febrile UTI urinary infection	0-2 years	3 42%	4 58%	6 37.5%	10 62.5%	23 19.8%
	2-5 years	5 83%	1 17%	9 50%	9 50%	24 20.7%
	<5 years	7 53.8%	6 46.2%	29 51.7%	27 48.3%	69 59.5%
	Total	15 57%	11 43%	44 48%	46 52%	116 21%

UTI: Urinary tract infection, VUR: vesicoureteral reflux

Considering all of the variables, pathologic findings detected by RBUS seem to increase the possibility of encountering higher grade VURs in VCUG, and increased renal echogenicity suggests the highest diagnostic accuracy for high-grade VUR with odds ratio of 1.9, followed by dilated ureter, parenchymal thinning, and presence of hydronephrosis. Here, we present the first study that evaluates renal parenchymal thickness and renal echogenicity detected on RBUS as predictors of VUR in patients who experienced VCUG. Parenchymal thinning was a predictive finding for children under 2 years of age as well as in children over 5 years of age. Especially in children older than 5 years, if the parenchymal thinning was detected using ultrasonography, the probability of reflux should be considered.

In this study, no significant difference is detected when comparing gender and presence of VUR in all age groups between the patients who had a first febrile urinary tract infection and the patients who had recurrent febrile urinary tract infections.

Study Limitations

The major limitation of our study is its retrospective nature. Also, the data are from a single referral children's hospital. We also included VCUG examinations performed only in one year. Finally, we did not evaluate renal scintigraphy findings, although this would provide more information about renal functions and scars. The strength of our work can be defined as increased statistical power according to the large number of participants.

Conclusions

In conclusion, abnormal RBUS findings, such as hydronephrosis, parenchymal thinning, and increased echogenicity, have a higher probability of VUR, and these findings can be affected by the age of the child patient. In children younger than 2 years, thinned renal parenchyme predicted findings for VUR. There was no significant difference in predicting the presence of VUR among the RBUS findings in children at 2-5 years of age. Thinned parenchymal and moderate to severe hydronephrosis were significantly correlated with the presence of reflux for the children older than 5 years. High-grade VUR was 1.9 times higher in renal echogenicity with dilated ureter, parenchymal thinning, and presence of hydronephrosis. The results of our study show that all ultrasonographic findings need to be taken into account when evaluating a child with the suspicion of reflux to avoid unnecessarily performing invasive VCUGs.

Ethics

Ethics Committee Approval: Permission from the Ethics Committee (number 2018-128) was obtained from the Ankara City Hospital, Child Health and Diseases, Hematology and Oncology Training and Research Hospital.

Informed Consent: Consent form was obtained from the patients' families.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.T.T., D.G., S.A.B., G.D., Concept: D.G., H.T.T., Design: H.T.T., G.D., Data Collection or Processing: G.D., Analysis or Interpretation: S.A.B., Literature Search: D.G., G.D., Writing: D.G., H.T.T.

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