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Original Article

Voiding cystourethrogram: How much should we be selective?

İşeme sistoüretrografisi: Ne kadar seçici olmalıyız?

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ABSTRACT

Objective: In this study, we examined the patients' characteristics, who underwent voiding cystourethrography (VCUG), in order to determine any selectivity for indication of this invasive method.

Material and methods: After exclusion of indications of neurogenic bladder or antenatal hydronephrosis and control VCUGs, 159 VCUGs performed in our clinic within one year were evaluated. Patients are divided into three groups accoding to age. Clinical characteristic and findings of renal ultrasonography (US) and renal scintigraphy were examined.

Results: Vesicoureteral reflux (VUR) was detected in 61 (38.3%) of 159 patients who underwent cystourethrographic examinations, in 45.8% of the patients with a history of recurrent urinary tract infection (UTI), in 22.0% of the patients with pathological urinary system US without history of recurrent UTI. High-grade reflux rate was significantly more frequent in renal units with pathological US findings. Severe scar was significantly more frequent in renal units with high-grade reflux when compared to renal units without reflux and those with low-grade reflux. Predictive values of recurrent UTI, scarring status and pathological US for VUR were separately analyzed and seen that likelihood of indicating VUR was increased when all 3 risk factors were assessed together.

Conclusion: Vesicoureteral reflux is a problem in which diagnostic process and management strategy should have to be considered in individualized manner for each patient. Before prescribing invasive VCUG, imaging urinary system by US and scintigraphy and determining whether there is recurrent UTI will improve selectivity and success of VCUG.

Keywords: Children; urinary tract infection; voiding cystourethrography.

ÖZ

Amaç: Bu çalışmada, invaziv bir işlem olan işeme sistoüretrografisi (VSUG) endikasyonunda herhangi seçicilik belirleyebilmek için, işlem yapılan hasta özelliklerini inceledik.

Gereç ve yöntemler: Nörojenik mesane, antenatal hidronefroz endikasyonları ve kontrol VSUG çekimleri dışlandıktan sonra kliniğimizde bir yıl içinde yapılan 159 VSUG incelendi. Hastalar yaş, klinik özellikler ve renal ultrasonografi (US) bulgularına göre üç gruba ayrıldı ve renal sintigrafileri incelendi.

Bulgular: Sistoüretrografi çekilen 159 hastanın 61'inde (%38,3), rekürren idrar yolu enfeksiyonu (RİYE) hikayesi olan hastaların %45,8'inde, RİYE olmaksızın anormal üriner sistem US olanların %22'sinde vezikoüretal reflü (VUR) tespit edildi. Yüksek dereceli reflü oranı anormal US bulgusu olan renal ünitelerde anlamlı olarak yüksekti. Ciddi renal skar bulgusu yüksek dereceli reflü olanlarda reflü olmayan ya da düşük dereceli olanlara kıyasla anlamlı olarak yüksekti. Skar durumu, RİYE ve anormal US bulgularının VUR için ayrı ayrı öngörü değerleri analiz edildi ve her üç risk faktörünün birlikte değerlendirilmesi ile VUR'a eşlik etme öngörü olasılığının arttığı görüldü.

Sonuç: Vezikoüreteral reflü, tanısal yaklaşım ve süreçte her hastaya bireyselleştirilmiş bir şekilde değerlendirme gerektiren bir problemdir. İnvaziv bir VSUG istemeden önce üriner sistemin US ve sintigrafi ile görüntülenmesi ve RİYE olup olmadığının belirlenmesi VSUG'de hedef başarıyı ve seçiciliği iyileştirecektir.

Anahtar Kelimeler: Çocuk; üriner sistem enfeksiyonu; işeme sistoüretrografisi.

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Introduction

Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder into the upper urinary tract and it is commonly seen in pediatric nephrology and urology practice. The prevalence of reflux is estimated to be 1%, whereas 30-50% of the children with recurrent urinary tract infection (UTI) have VUR.[1,2] It is known that there is a strong relationship between UTI and VUR.

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Delayed diagnosis or inadequate treatment may result in recurrent UTI, hypertension, developmental delay, reflux nephropathy and chronic kidney disease.[3]

The diagnosis of VUR is based upon the demonstration of reflux of urine from the bladder to the upper urinary tract using contrast-enhanced voiding cystourethrography (VCUG) which is an invasive method and has some disadvantages like radiation exposure, hypersensitivity to radiocontrast agents and dysuria. Therefore, it is important to be careful about the indication of the procedure.[4,5]

In order to determine any selectivity for the indication of VCUG, this study examined the characteristics of the patients who underwent VCUG.

Material and methods

All children referred to our clinic from January 1, 2010 to December 31, 2010 with recurrent urinary tract infection and/or pathological renal ultrasonography findings were reviewed retrospectively. Children with neurogenic bladder, antenatally detected hydronephrosis, previously performed subureteric injection and inadequate data obtained from VCUG were excluded from the study. Thus, final analysis included data of 159 patients. The procedures were performed under fluoroscopic guidance (Fluoroscope: Axiom; Siemens, Forcheim, Germany). Before VCUG procedure informed, and undersigned consent forms were obtained from all patients.

Demographic data and clinical findings of the patients including age, gender, chief complaints at presentation, presence of recurrent UTI, constipation, urinary incontinence were obtained from medical records. Patients who experienced one episode of pyelonephritis were included in the recurrent UTI group. Renal ultrasound (US) and scintigraphy findings were harvested.

Urinary tract infection was defined based on the results of urine culture as the growth of a single pathogen of more than 10^5 -colony forming units (CFU)/mL. Urine samples were collected from infants in sterile urine bags or midstream clean catch method from toilet trained patients. Recurrent UTI was defined as an episode of pyelonephritis or at least three episodes of lower UTI.

Patients were divided into three groups according to their ages at the time of VCUG: Group 1, 55 infants (<2 yr); Group 2, 38 children (2-5 yr); Group 3, 66 children (>5 yr). Groups 2 and 3 consisted all toilet- trained patients. Renal scar was evaluated by dimercaptosuccinic acid renal scintigraphy (DMSA) based on the criteria of Goldraich et al.[6]. Children with stage 1 or 2 scarring were defined as having low grade scar, while those with stage 3 or 4 scarring as having severe scar. 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 based on the International Classification of Vesicoureteral Reflux.[7] All conditions, and phases of our study were conducted in accordance with Helsinki Declaration.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 22.0 (SPSS IBM Corp, Armonk, New York, USA). The comparisons of proportions were performed with the *chi*-square tests. To assess the selectivity of each of the three conditions (recurrent UTI, renal scarring and pathological ultrasonographic findings) for VUR, the sensitivity, specificity, positive predictive and negative predictive values were determined. Concordance between VUR and recurrent UTI, renal scarring, pathological ultrasonographic findings were assessed using Cohen's kappa coefficient and McNemar test. Values for kappa ranged from 0 to 1.00, with higher values indicating better agreement. To predict the probability of VUR binary logistic regression analysis was done. Level of statistical significance was set at p value of <0.05.

Results

Distribution of gender, status of VUR and scarring in the age groups are presented in Table 1. Sixty-one patients had primary VUR. We did not detect VUR in 209 renal units. Eighty-one units had VUR. Any other associated abnormality was not detected. There was female predominance in all age groups which became more prominent by age. When VUR was assessed according to age groups, incidence of VUR was significantly higher in Group 2 compared to Groups 1 and 3 ($p<0.05$). However, no significant difference was detected between Groups 1 and 3 ($p>0.05$). DMSA renal scintigraphy for the evaluation of scarring was obtained in 145 children. 127 of them had mild to severe scarings. The number of the children with severe renal scar was significantly higher in Group 2 compared to Groups 1 and 3 (Table 1, $p<0.05$).

History of recurrent UTI, which detected in 68.5% of the patients, was leading indication of VCUG. The rest of the patients (31.5%) had urinary system abnormalities in US without recurrent UTI (Table 2). VUR was detected in 61 (38.3%) of 159 patients underwent VCUG. VUR was detected in 45.8% of the patients with history of recurrent UTI, whereas in 22.0% of the patients with pathological urinary system US findings without history of recurrent UTI (Table 2; $p<0.05$).

Urologic abnormality on US was detected in 52 patients with recurrent UTI. 53.8 % of them had VUR (Table 2). The prevalence of

Table 1. Gender distribution, presence and degree of VUR and renal scarring according to age groups

	Group 1	Group 2	Group 3
Gender F/M (F ratio %)	30/25 (54.5)	26/12 (68.4)	48/18 (72.7)*
VUR n/n (%)	18/55 (33)	21/38 (55)*, **	22/66 (33)
High grade reflux, n	5	9	7
Severe scarring/total scarring, n/n(%)	16/45 (36)	18/29 (62)*,**	19/53 (36)

*p<0.05 vs. Group 1, **p<0.05 vs. Group 3
F: female; M: male; VUR: vesicoureteral reflux

VUR was significantly higher in patients with recurrent UTI and normal urinary system US compared to patients with abnormal US findings without recurrent UTI (Table 2; p=0.04).

Assessment of VUR and its severity according to gender

The incidence of VUR was 31.6% in girls and 39.3% in boys. The prevalence of high-grade reflux was 30.0% in girls and 41.6% in boys. There was no significant difference between genders in terms of the incidence and severity of VUR.

Evaluation of the relationship between scintigraphy findings and VUR

To evaluate relationship between presence and severity of renal scarring, and VUR on DMSA scan, we separately analyzed each renal unit. Overall, 290 renal units were assessed in 145 patients who had DMSA scan. Of 209 renal units without reflux, 71 (34%) had no evidence of renal scar formation, 105 (50.3%) had mild, and 33 had severe scarring on DMSA scan.

No scarring was detected in 18 (30%) cases while low grade scarring was detected in 29 (48.4%) patients. Severe scarring was detected in 13 (21.6%) of 60 renal units with low-grade reflux. No scarring was detected in only one (4.8%) while low grade scarring was detected in 3 (14.3%) renal units. Severe scarring was found in 17 (80.9%) of 21 renal units with high-grade reflux (Table 3).

There was no significant difference between renal units without VUR and those with low-grade reflux in terms of the presence and severity of renal scarring. However, the number of renal units with severe scarring was significantly higher among renal units with high-grade reflux compared to renal units without reflux or with low-grade reflux (p<0.05; Table 3).

Evaluation of the relationship between the findings of ultrasonography and VUR

Voiding cystourethrography was unremarkable in 160 (78.0%) of 205 renal units with normal renal US. However, 41 of them (20%) had low, and 4 (2%) cases high grade refluxes.

Voiding cystourethrography did not reveal VUR in 71 (63.0%) of 113 renal units with pathological US findings. It showed low, and high -grade refluxes in 25 (22.0%), and 17 (15.0%) renal units, respectively (Table 4).

There was no significant difference between renal units with or without pathological US findings in terms of the absence of reflux or presence of low-grade reflux while high-grade reflux was significantly more frequent in renal units with pathological US findings (p<0.05; Table 4).

Assesment of the probability of VUR

To evaluate the predictive values of recurrent UTI, renal scarring on DMSA and pathological renal US findings for VUR, we separately analyzed 318 renal units in which VUR was evaluated by VCUG. Cohen kappa analysis showed weak concordance between VUR and 3 risk factors (3 risk factors=recurrent UTI, renal scarring, and pathological US findings) when assessed separately. (Cohen kappa values: 0.133, 0.059 and 0.160 for recurrent UTI, scarring status and pathological renal US findings, respectively) (Table 5). Logistic regression model for probability of VUR is presented in Table 6. The results indicated that probability of VUR increased when all 3 risk factors were assessed together (Table 6).

Table 2. Indications of VCUG and VUR

Indications of VCUG	Number of patients withVUR (+)/number of total patients n/n (%)
Recurrent UTI	50/ 109 (5.8)*
Recurrent UTI with normal ultrasound	22/ 57 (38.5)*
Recurrent UTI with pathological ultrasonography	28/ 52 (53.8)*
Pathological ultrasonography without recurrent UTI	11/ 50 (22)
Total	61/ 159 (38.3)

*p<0.05, vs. patients with pathological ultrasonography without recurrent UTI
VCUG: voiding cystouretrography; VUR: vesicoureteral reflux; UTI: urinary tract infection

Table 3. The relationship between the presence of scar in scintigraphy and the severity of VUR

	The severity of VUR			
Severity of scar	No reflux	Low- grade reflux	High- grade reflux	Total
No scarring	71 (34%)	18 (30%)	1 (4.8%)	90
Low grade scarring (Goldraich 1,2)	105 (50.3%)	29 (48.4%)	3 (14.3%)	137
Severe scarring (Goldraich 3,4)	33 (15.7%)	13 (21.6%)	17 (80.9%)*	63
Total	209	60	21	290

*p<0.05 vs. patients without VUR with severe scarring and patients with mild- grade reflux and severe scarring
VUR: vesicoureteral reflux

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Table 4. The relationship between the findings of renal ultrasound and the severity of VUR

	The severity of VUR			
Severity of scar	**No reflux**	**Low- grade reflux**	**High- grade reflux**	**Total**
No scarring	71 (34%)	18 (30%)	1 (4.8%)	90
Low grade scarring (Goldraich 1,2)	105 (50.3%)	29 (48.4%)	3 (14.3%)	137
Severe scarring (Goldraich 3,4)	33 (15.7%)	13 (21.6%)	17 (80.9%)*	63
Total	209	60	21	290

*p<0.05 vs. patients with high- grade reflux and normal renal ultrasound
VUR: vesicoureteral reflux

Table 5. The concordance between VUR in renal units and recurrent UTI, renal scarring, pathological ultrasonography

	VUR			Cohen kappa					
Risk faktors	**Positive (n)**	**Negative (n)**	**Total**	**p value**	**Cohen kappa**	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
Recurrent UTI									
Positive (n)	72	146	218						
Negative (n)	15	85	100	0.0008	0.133	33	85	82.7	36.8
Renal scarring									
Positive (n)	68	160	228						
Negative (n)	19	71	90	0.1164	0.059	29.8	78.8	78	30
Pathological US									
Positive (n)	42	71	113						
Negative (n)	45	160	205	0.0036	0.160	37	78	48	69
Total	87	231	318						

PPV: positive predictive value; NPV: negative predictive value; VUR: vesicoureteral reflux; UTI: urinary tract infection; US: ultrasound

Discussion

The present study indicates that the rate of VUR is high in patients with recurrent UTI, renal scar and pathological renal US findings. Vesicoureteral reflux is the most common urinary system anomaly in childhood.[8] To assess younger children and infants for VUR after acute piyelonephritis is highly recommended. However, there is no consensus on timing and indication of VCUG.[9,10] Gonadal radiation exposure is the main reason for restricting the use of VCUG.[11]

Clinically, VUR is generally identified for the evaluation of antenatal hydronephrosis or recurrent UTI.[12] In our study, patients with antenatal hydronephrosis were excluded, because VCUG is mostly performed in these patients as a part of routine evaluation. The main goal of this study was to determine the more selective indications of VCUG. Thus, exclusion of such patients could have positive effect on the interpretation of data.

Table 6. Prediction of the probability of vesicoureteral reflux

Risk factors	**Number of renal units (%)**	**Probability of VUR**
No	12 (3.8)	0.07092
Renal scarring alone	37 (11.6)	0.09538
Pathological ultrasonography alone	13 (4.1)	0.17050
Renal scarring and pathological ultrasonography	38 (11.9)	0.22114
Recurrent UTI alone	58 (18.2)	0.22222
Recurrent UTI and renal scarring	98 (30.8)	0.28297
Recurrent UTI and pathological ultrasonography	7 (2.2)	0.43483
Recurrent UTI and renal scarring and pathological ultrasonography	55 (17.3)	0.51521
Total	318 (100.0)	

UTI: urinary tract infection; VUR: vesicoureteral reflux

In this study, there was a female predominance. As for the presence of VUR, number of girls was significantly higher than boys in all age groups which became more prominent by age. This finding resulted from the fact that majority of our patients (68.5%) underwent VCUG as a part of screening of recurrent UTI which is more common in girls at all ages except the first year of life. Incidence of UTI increases in favor of girls with age.

There is an ongoing debate whether patients should be selected for VCUG or not. It is an invasive method with considerable risk for radiation exposure.[13] The most common indications of VCUG include recurrent UTI and voiding dysfunction. In this study, most of the children had VCUG because of the recurrent UTI. Rate of the detection of VUR depends on age, gender and clinical presentation at the time of the diagnosis of UTI.[14,15] Vesicoureteral reflux was detected in 19-21.6% of the patients younger than 10 years after the first UTI.[9,16] In our study, VUR was detected in 61 (38.3%) of 159 patients who underwent VCUG. More than half of (53.8%) the patients with recurrent UTI and pathological renal US findings had VUR. Our findings indicated that probability of VUR is higher in the concurrent presence of UTI and pathological renal US findings. Thus, we think that VCUG should be done for these patients.

There is a well-known relationship between recurrent UTI and VUR. Presence of recurrent UTI increases likelihood of VUR in all age groups.[14] Routine VCUG assessment in patients with UTI has always been questioned.[14,15,17-19] At this point, contrary to 1999 American Academy of Pediatrics (AAP) guideline that recommends VCUG in all children having pyelonephritis at 2-24 months of age, 2011 AAP guideline abolished routine VCUG recommendation after febrile pyelonephritis episode in children aged 2-24 months unless atypical clinical course, pathological US findings and renal scarring exist. Thus, a profit-income account was performed by preventing unnecessary anxiety and radiation exposure while taking the risk of likelihood of missing reflux in a small number of patients into account.[20] However, it remains unclear whether the benefits of detection and treatment of VUR outweigh the risks. Tseng et al.[21] recommended renal scintigraphy and avoided VCUG after the first febrile episode of pyelonephritis in the absence of renal scarring. They reported that unnecessary VCUGs could be prevented by 30% in this way. It is known that the risk for renal scarring is higher in patients with VUR compared to those without. Increase of the severity of reflux also increases the risk for renal scarring.[22-25] Renal scintigraphy can detect the majority of the patients with moderate to severe reflux (grade 3 or higher).[21,26] Our findings also indicated the presence of a relationship between high-grade VUR and renal scarring. In our study, renal scarring was found relatively more frequently in patients aged 25-60 months with high VUR frequency. We also think that presence of renal scarring might be an indicator for the presence of VUR.

Although urinary US is considered to be the first-line imaging modality in the conventional follow-up strategy of children with UTI, it has a low diagnostic value in the detection of VUR. In the study by Mahant et al.[27] 60% of the patients with VUR had normal urinary US. There were pelvicalyceal and/or ureteral dilatation in 24% of the patients without VUR. They also found that sensitivity, specificity, positive predictive and negative predictive values of US were 40%, 76%, 32% and 82%, respectively. Our findings were similar to those found in Mahant's study. We have shown that patients with normal sonographic findings had low-grade reflux. If the patients had renal units with pathological renal US findings, higher rates of probability and severity of reflux were detected.

In our study, VUR frequency was found to be high in patients with recurrent UTI compared to those with pathological renal US findings without recurrent UTI. In addition, significant differences were detected in the frequency of VUR between patients with or without scarring on scintigraphy, between patients with or without pathological renal US findings and between patients aged 25-60 months and other age groups. One or more of the conditions referred to above may be present in some renal units. Therefore, it was attempted to evaluate the relevance of recurrent UTI, pathological renal US findings, and the presence of scarring in demonstrating the presence of reflux. When a further evaluation was performed to elucidate which abnormality can be a more reliable predictor of reflux, presence of UTI alone was more predictive than the presence of pathological renal US findings, and scarring. These risk factors alone had a weak correlation with the presence of vesicoureteral reflux and likelihood of VUR increased when all 3 risk factors were assessed together.

There was some limitations of our study. Due to its retrospective nature, patient data including status of antibiotic prophylaxis or lower urinary tract symptoms of toilet trained patients were not available. In conclusion, vesicoureteral reflux is a problem in which diagnostic process and management strategy should be considered as a unique case for each patient. Imaging urinary system by sonography and scintigraphy, determining whether there is recurrent UTI or not will improve selectivity for VCUG.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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