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Uroepithelial Thickening Improves Detection of Vesicoureteral Reflux in Infants with Prenatal Hydronephrosis

Zachary N. Gordon¹, Daryl J. McLeod^{1,2}, Christina B. Ching^{1,2}, Daniel B. Herz^{1,2}, D. Gregory Bates⁴, Brian Becknell³, and Seth A. Alpert^{1,2}

¹The Ohio State University Wexner Medical Center, Department of Urology, Columbus, OH

²Nationwide Children's Hospital, Section of Pediatric Urology, Columbus, OH

³Nationwide Children's Hospital, Section of Nephrology, Columbus, OH

⁴Nationwide Children's Hospital, Department of Radiology, Columbus, OH

Summary

Introduction/Background—Postnatal evaluation of prenatal hydronephrosis (PNH) often includes VCUG for VUR assessment. Despite limited supporting data, VCUG is currently recommended if postnatal RBUS reveals moderate/severe hydronephrosis (HN) or hydroureter (HU). Recent studies have shown VUR is more accurately diagnosed by using certain sonographic findings as criteria for obtaining VCUG. Uroepithelial thickening (UET) of the renal pelvis is a finding associated with high-grade VUR (HGVUR); however, the clinical significance of UET with PNH has not been studied.

Objective—We sought to determine if the presence of UET implies increased risk for VUR, and to investigate whether UET can improve the test characteristics of RBUS for VUR.

Study Design—We retrospectively analyzed postnatal RBUS and VCUG findings in infants 30 days undergoing evaluation for “prenatal hydronephrosis” over an 11-year period. We used logistic regression to identify factors associated with VUR. Test characteristics of RBUS for HGVUR were compared based on the presence of UET and two criteria sets to define abnormal RBUS. Criteria set 1 consisted of HN SFU grade 3–4 and/or HU; criteria set 2 was defined by the presence of two of following: UET, HU, duplication, and/or renal dysmorphism.

Results—Of 135 patients, 39 (29%) had VUR, of whom 16 (41%) had HGVUR. UET was significantly associated with VUR ($p < 0.001$), and the sensitivity for HGVUR based on UET alone was 94%. On multivariable analysis, UET, HU, duplication, and renal dysmorphism remained significant independent predictors of HGVUR. Compared to criteria 1, using criteria 2 resulted in 43 fewer VCUGs, and significant improvement in the sensitivity and specificity for HGVUR.

Discussion—Consistent with previous studies, HN alone on postnatal RBUS has little value in predicting the presence or severity of VUR. This study is the largest known series to evaluate UET in the setting of PNH, and our results demonstrate that UET, as well as HU, duplication and renal dysmorphism, are independent sonographic findings predicting HGVUR. Using our proposed

criteria, the probability of HGVUR is fourfold more than the prevalence described in the literature, and importantly, when compared to the criteria recommended by the SFU and AUA, would have resulted in 53% fewer VCUGs while missing zero cases of HGVUR.

Conclusion—In infants with PNH, the sonographic findings of UET, HU, duplication and renal dysmorphism independently indicate greater risk of HGVUR, and the sensitivity and specificity of RBUS for HGVUR is markedly improved when at least two of the four are present.

Summary Table

High-Grade VUR	Multivariable Analysis		
	OR	95% CI	p-value
Uroepithelial Thickening	54.45	4.97-597.0	0.001
Hydroureter	5.35	1.24-22.99	0.024
Duplication	10.78	2.21-52.57	0.003
Renal Dysmorphism	14.23	2.17-94.37	0.006
Criteria 1*	Presence of VUR	Absence of VUR	Total
Positive RBUS	24	57	81
Negative RBUS	15	39	54
Totals	39	96	135
Criteria 2*	Presence of VUR	Absence of VUR	Total
Positive RBUS	21	17	38
Negative RBUS	18	79	97
Totals	39	96	135
Test Characteristics of RBUS for HGVUR	Criteria 1	Criteria 2	UET
Sensitivity	88%	100%	94%
Specificity	44%	82%	57%
PPV	17%	42%	23%
NPV	96%	100%	99%
LR+	1.57	5.41	2.19
LR-	0.27	0	0.11
OR (95% CI)	5.43 (1.18-24.97)	143.00 (8.27-2473.74)	20.00 (2.56-156.38)

*Criteria 1: presence of HN SFU grade 3-4 or HU

Criteria 2: presence of at least two of the following: UET; HU; duplication; renal dysmorphism.

Keywords

Vesicoureteral Reflux; Prenatal Hydronephrosis; Uroepithelial Thickening; Hydroureter; Renal Bladder Ultrasonography

Introduction

Postnatal radiographic evaluation of prenatal hydronephrosis (PNH) often includes voiding cystourethrography (VCUG) to assess for vesicoureteral reflux (VUR). Both the 2010 Society for Fetal Urology (SFU) consensus statement on PNH and the 2010 American Urological Association (AUA) Clinical Practice Guideline (CPG) on screening for VUR in infants with PNH recommend VCUG if postnatal renal bladder ultrasonography (RBUS) reveals either moderate/severe (SFU grade 3-4) hydronephrosis (HN) or hydroureter (HU) [1,2]. However, there continues to be ongoing debate regarding who may benefit from VCUG and whether detection of VUR in asymptomatic patients will ultimately be clinically significant. Several studies correlating the degree of HN with VUR prevalence suggest that only higher grades of HN may warrant evaluation. However, results have been inconsistent and trend toward no association between HN grade and VUR prevalence [3-5]. Nevertheless, in the setting of PNH, VCUG is still performed at a high rate with a large number of negative examinations.

A recent study using the findings of hydroureter (HU), renal dysmorphia and/or duplication on postnatal RBUS as criteria for obtaining a VCUG has shown that VUR can be detected more specifically in this population [6]. Uroepithelial thickening (UET) of the renal pelvis is a sonographic finding that has been associated with inflammation, prior distention, urinary tract infection (UTI), urolithiasis, rejection after renal transplantation, VUR, and obstruction [7-16]; however, the clinical significance and implications of this finding in the setting of PNH have not been studied. As our previous work has demonstrated that UET is strongly associated with HGVUR in the setting of first febrile UTI in young children [17], we hypothesized that UET might also be a significant independent predictor of HGVUR in the postnatal evaluation of PNH. We sought to determine if the presence of UET on initial postnatal RBUS in the setting of PNH is an additional finding that implies a greater risk for VUR, and to investigate whether UET can improve the test characteristics of RBUS for high-grade VUR (HGVUR).

Patients and Methods

Following institutional review board approval, we identified all infants < 30 days who had undergone RBUS for the indication of “prenatal hydronephrosis” at our institution from December 2002 to December 2013. RBUS studies with the non-specific indication of “hydronephrosis” were excluded. Cases were limited to those who had a VCUG obtained within 90 days of RBUS, and whose images from both studies were available for review within our institution's medical records. Prenatal RBUS were not evaluated given the limited accessibility to these studies performed elsewhere. Patients with spina bifida, posterior urethral valves, or history of UTI were excluded. Both a senior pediatric radiologist and

urologist reviewed all imaging and radiology reports. Age at RBUS and presence of UET, HN, HU, duplication, renal dysmorphia, and VUR were recorded.

UET was defined as wall thickening measuring ≥ 1 mm, appearing as a hypoechoic rim within the renal pelvic wall delineated on each side by a thin hyperechoic line [7,11,13-15,17]. HN was graded based on SFU criteria [1,18]. HU included any degree of ureteral dilatation visualized on RBUS. Renal dysmorphia was defined as a hyperechogenic kidney or significant renal hypotrophy. VUR was detected by means of VCUG, and classified using the international VUR grading system [19]. Low-grade VUR (LGVUR) was defined as grade 1-3 and HGVUR as grade 4-5.

We used two sets of criteria to define an abnormal RBUS. In criteria set 1, RBUS was considered abnormal if there was evidence of HN SFU grade 3-4 and/or HU, consistent with the 2010 SFU consensus statement on PNH and the 2010 AUA CPG on screening for VUR in infants with PNH [1,2]. In criteria set 2, RBUS was considered abnormal if there was evidence of any two of the following: UET, HU, duplication, or renal dysmorphia.

Categorical data were analyzed using Fisher exact test or chi-square test. Continuous data were analyzed using Mann-Whitney *U* test. Univariable and multivariable logistic regression were used to identify factors associated with VUR. Odds ratios (OR) and 95% confidence intervals (CI) for prediction of HGVUR were calculated. Test characteristics of RBUS, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-), for VUR and HGVUR were calculated based on presence of UET, criteria 1, and criteria 2. Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

During an 11-year period, 410 patients underwent RBUS for the indication of “prenatal hydronephrosis.” Of these, 206 infants were ≤ 30 days, and 135 met inclusion criteria. Of the 135 patients included, 39 (29%) had VUR, of whom 23 (59%) had LGVUR and 16 (41%) had HGVUR. Neither gender, age at RBUS, HN grade, HU, duplication, nor renal dysmorphia were associated with the presence of any VUR, whereas HN SFU grade 3-4, HU, duplication, and renal dysmorphia were all associated with the presence of HGVUR (Table 1). In addition, the finding of UET was significantly associated with the presence of any VUR ($p < 0.001$), VUR grade 4 ($p = 0.031$) and VUR grade 5 ($p = 0.003$), but not LGVUR ($p = 0.207$) (Table 2). On multivariable analysis, UET and duplication remained significant independent predictors of any VUR, whereas UET, HU, duplication, and renal dysmorphia all remained significant independent predictors of HGVUR (Table 3). The test characteristics of RBUS for VUR and HGVUR based on presence of UET, criteria 1, and criteria 2 are compared in Table 4. The sensitivity and specificity of UET for any VUR was 74% and 94%, respectively, and 94% and 57%, respectively, for HGVUR. Compared to UET, criteria 1 was both less sensitive and less specific for any VUR as well as HGVUR. In contrast, the test characteristics of criteria 2 for HGVUR were superior to UET, with a sensitivity and specificity of 100% and 82%, respectively (Table 4).

RBUS was abnormal in 81 patients (60%) based on criteria 1, whereas it was only considered abnormal in 38 patients (28%) based on criteria 2. If VCUG was obtained based only on criteria 1, then 2 children with HGVUR and 13 with LGVUR would have been missed. In contrast, using criteria 2, 43 fewer VCUGs would have been obtained, and no infants with HGVUR and only 18 with LGVUR would have been missed. Assuming a prevalence of HGVUR of 5-10% in patients diagnosed with PNH [2,6,20], we calculated a post-test probability of 23% to 38%. The calculated post-test probability for a negative test was 0%. When RBUS was abnormal based on criteria 2, the odds ratio of detecting HGVUR was 143 (95% CI 8.27-2473).

Discussion

Studies evaluating RBUS as a screening tool for VUR in infants with a history of PNH are limited and findings have varied widely [21-23]. Although both the SFU and AUA recommend VCUG if postnatal RBUS reveals either HN SFU grade 3-4 or HU, both also acknowledge the lack of strong data to support these recommendations [1,2]. In fact, a previous meta-analysis investigating the risk of postnatal pathology in PNH found no association between degree of HN and detection of VUR [23]. Our results confirm these findings and suggest that HN alone on postnatal RBUS is a poor predictor for either the presence or severity of VUR.

In an attempt to detect VUR more specifically in patients with PNH, Lee *et al.* analyzed the ability of postnatal RBUS findings to predict VUR on subsequent VCUG. By using ultrasonography criteria of HU, duplication and renal dysmorphism to determine the need for VCUG, they found that VUR would have been missed in 33% of LGVUR and in 17% of HGVUR, yet this appeared to be of low clinical significance. Moreover, when compared to using HN SFU grade 3-4 as the trigger for obtaining a VCUG, their proposed criteria would have resulted in 40% fewer VCUGs with an almost identical miss rate [6]. Consistent with these findings, our study demonstrates that HU, duplication and renal dysmorphism are all significant independent predictors of HGVUR.

In addition to confirming the findings of previous investigators, our study is the largest known series to evaluate the significance of UET on postnatal RBUS in the setting of PNH. Several studies in the past two decades have reported an association between UET and VUR, and most have concluded that UET is an abnormal, but non-specific finding on RBUS [7,8]. The majority of these studies also have significant limitations, such as using contralateral renal units to serve as controls and/or omitting the grade of VUR [8,13,14]. While our previous work demonstrated the sonographic finding of UET is strongly associated with HGVUR in the setting of first febrile UTI in young children [17], these new results clearly demonstrate that UET is also a significant independent predictor of HGVUR in the postnatal evaluation of PNH. Moreover, Fan and Tain [11] found that persistent UET in consecutive RBUS had a strong association with VUR, particularly HGVUR. On multivariable logistic regression analysis, which included UET, hypoplastic kidney, nephromegaly, HN, HU, and bladder wall thickening as cofactors, persistent UET was the only finding on RBUS associated with HGVUR (OR 8.9, 95% CI 2.3-34.9, $p < 0.002$). Although the indication for RBUS was not limited to PNH in their study, their results are also consistent with our

findings that UET is an independent predictor of HGVUR (OR 54.45, 95% CI 4.97-597.0, $p=0.001$).

Although the natural history of VUR diagnosed during evaluation of PNH likely differs from that diagnosed after a febrile UTI, with the former seemingly having a more benign course with a higher rate of spontaneous resolution [24], tailoring the use of VCUG to those at high risk is still beneficial given the risks of VCUG catheter-related UTI, radiation exposure, and patient discomfort. Based on our findings, VCUG would be limited to those at highest risk of HGVUR if it were ordered when two of the following findings are present on postnatal RBUS: UET, HU, duplication and renal dysmorphia. Collectively, the probability of actually having HGVUR with 2 of these 4 RBUS findings is fourfold as high as the prevalence described in the literature [2,6,20]. Importantly, when compared to using HN SFU grade 3-4 or HU (i.e. criteria 1), as recommended by the SFU and AUA [1,2], to determine need for VCUG, our proposed criteria (i.e. criteria 2) would have resulted in 43 (53%) fewer VCUGs while missing zero cases of HGVUR. While the sensitivity of detecting HGVUR based on the finding of UET alone was 94%, the specificity was only 57% and one case of HGVUR was still missed. Moreover, using UET alone to determine need for VCUG would have resulted in only 15 (19%) *fewer* VCUGs when compared to criteria 1 and 28 (74%) *more* VCUGs when compared to criteria 2.

Our study does have several limitations, most of which are associated with the retrospective design. For example, our study includes a large number of patients followed at community practices and seen at our institution only for imaging. Although “prenatal hydronephrosis” was the indication for RBUS in all patients, many of these diagnoses were made elsewhere outside our institution and could not be independently verified by review of the prenatal ultrasound images. As some patients may have been misclassified, the results may not reflect those that might have been seen among infants who had strictly defined and independently-confirmed PNH. However, irrespective of the diagnostic details, these are the patients being referred for imaging, and therefore, reflect the “real-world” screening population seen in practice. Our study is also limited by its relatively small sample size with some selection bias due to our exclusion criteria. As we excluded all RBUS studies ordered for the non-specific indication of “hydronephrosis” as well as patients who did not undergo VCUG, there is the possibility of missing data, particularly in those with PNH who had a postnatal RBUS ordered with an indication of only “hydronephrosis” rather than “prenatal hydronephrosis.”

Lastly, although our proposed criteria would miss several cases of LGVUR, it is generally agreed that children with LGVUR are at low risk for renal damage, with a risk for UTI similar to that of children without VUR [25,26]. In contrast, the risk of pyelonephritis and subsequent scarring is substantially higher in patients with HGVUR, as shown in a large meta-analysis conducted by Shaikh *et al.* [27]. Thus, while the impact on clinical management was not evaluated in this study, the missed cases of LGVUR are likely of little clinical significance, given that those with HGVUR have the greatest risk for subsequent febrile UTI and renal damage.

Conclusions

In infants with a history of PNH, the findings of UET, HU, duplication and renal dysmorphism on postnatal RBUS each independently indicate a greater risk of HGVUR. Although abnormal RBUS cannot reliably predict the presence of HGVUR, a completely normal RBUS can essentially rule out HGVUR with a high degree of certainty. Our results support the AUA and SFU recommendations to limit VCUG to patients with abnormal RBUS; however, several unnecessary VCUGs would still be done and several cases of HGVUR would be missed if RBUS is only considered abnormal based on HN SFU grade 3-4 or HU. In contrast, the sensitivity of RBUS for HGVUR is markedly improved if VCUG is ordered when two of the following findings are present: UET, HU, duplication and renal dysmorphism. Significant cost savings, reduction of parental anxiety and decreased radiation exposure can be achieved by limiting the use of VCUG for further evaluation of PNH using these criteria. Given the strong association of UET with HGVUR, we recommend the presence or absence of UET on RBUS should be routinely reported by radiologists. In addition, future recommendations from the pediatric urology community on screening for VUR in infants with PNH should consider including UET as an additional abnormal finding on postnatal RBUS that warrants VCUG [1,2].

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Patient Demographics and RBUS Findings: Association with VUR & HGVUR on VCUG

Table 1

HGVUR (n = 16)		LGVUR (n = 23)		Any VUR (n = 39)		No VUR (n = 96)		p-value [‡]	p-value ^Φ
Gender, n (%)	Male	12 (75)	17 (74)	29 (74)	69 (72)	0.769	1.000		
	Female	4 (25)	6 (26)	10 (26)	27 (28)				
Age in days, median (IQR)									
HN SFU grade 1, n (%)	1 (6)	2 (9)	3 (8)	3 (3)	14 (12)	0.771	0.935		
HN SFU grade 2, n (%)	3 (19)	12 (52)	15 (39)	44 (46)		0.434	0.057		
HN SFU grade 3, n (%)	6 (38)	7 (30)	13 (33)	25 (26)		0.393	0.385		
HN SFU grade 4, n (%)	6 (38)	2 (9)	8 (21)	24 (25)		0.578	0.209		
HN SFU grade 3-4, n (%)	12 (75)	9 (39)	21 (54)	49 (51)		0.768	0.048*		
UET, n (%)	15 (94)	14 (61)	29 (74)	37 (39)		<0.001*	<0.001*		
Hydroureter, n (%)	9 (56)	6 (26)	15 (39)	24 (25)		0.118	0.017*		
Duplication, n (%)	6 (38)	4 (17)	10 (26)	12 (13)		0.061	0.025*		
Renal dysmorphism, n (%)	5 (31)	0 (0)	5 (13)	5 (5)		0.152	0.002*		
HN SFU grade 3-4 and/or HU, n (%)	14 (88)	10 (44)	24 (62)	57 (59)		0.816	0.017*		
Any 2 of the following, n (%)									
- UET									
- Hydroureter	16 (100)	5 (22)	21 (54)	17 (18)		<0.001*	<0.001*		
- Duplication									
- Renal dysmorphism									

^Φ For presence of any VUR (HGVUR and LGVUR combined) compared to absence of VUR

[†] For presence of HGVUR compared to absence of HGVUR

* Difference was statistically significant

Table 2
Patient Demographics and Radiographic Findings: Association with UET on RBUS

	UET Present (n = 66)		UET Absent (n = 69)	Total (n = 135)	p-value
	Male	Female			
Gender, n (%)	50 (76)	16 (24)	48 (70)	98 (73)	0.420
Age in days, median (IQR)	14 (14)	5 (8)	13 (12)	13 (13)	0.680
HN SFU grade 1, n (%)	30 (46)	19 (29)	29 (42)	59 (44)	0.688
HN SFU grade 2, n (%)	12 (18)	31 (47)	20 (29)	32 (24)	0.140
HN SFU grade 3, n (%)	16 (24)	10 (15)	23 (33)	39 (29)	0.244
HN SFU grade 3-4, n (%)	7 (11)	35 (53)	3 (4)	10 (7)	0.201
Hydronephrosis, n (%)	29 (44)	10 (15)	10 (15)	39 (29)	<0.001*
Any VUR (all grades), n (%)	2 (3)	4 (6)	3 (4)	5 (4)	1.000
VUR grade 1, n (%)	8 (12)	7 (11)	5 (7)	13 (10)	0.337
VUR grade 2, n (%)	7 (11)	8 (12)	1 (1)	8 (6)	0.031*
VUR grade 3, n (%)	8 (12)	14 (21)	0 (0)	8 (6)	0.003*
VUR grade 4, n (%)	15 (23)	14 (21)	9 (13)	23 (17)	0.207
VUR grade 5, n (%)	1 (1)	15 (23)	1 (1)	16 (12)	<0.001*

* Difference was statistically significant

Table 3
Univariable and multivariable logistic regression analyses of RBUS findings predicting any VUR and HGVUR

Any VUR	Univariable		
	OR	95% CI	p-value
Uroepithelial thickening	4.62	2.02-10.58	<0.001*
Hydroureter	1.88	0.85-4.15	0.120
Duplication	2.41	0.94-6.18	0.066
Renal dysmorphia	2.68	0.73-9.83	0.138
HN SFU grade 3-4	1.12	0.53-2.36	0.768
Any VUR	Multivariable		
	OR	95% CI	p-value
Uroepithelial thickening	5.05	2.15-11.89	<0.001*
Duplication	2.96	1.06-8.29	0.039*
High-Grade VUR	Univariable		
	OR	95% CI	p-value
Uroepithelial thickening	20.0	2.56-156.4	0.004*
Hydroureter	3.81	1.31-11.13	0.014*
Duplication	3.86	1.23-12.09	0.020*
Renal dysmorphia	10.36	2.59-41.42	0.001*
HN SFU grade 3-4	3.16	0.96-10.34	0.058
High-Grade VUR	Multivariable		
	OR	95% CI	p-value
Uroepithelial thickening	54.45	4.97-597.0	0.001*
Hydroureter	5.35	1.24-22.99	0.024*
Duplication	10.78	2.21-52.57	0.003*
Renal dysmorphia	14.23	2.17-94.37	0.006*

* Difference was statistically significant

Table 4
Test Characteristics of RBUS for VUR & HGVUR based on presence of Criteria* 1, 2, or UET

Criteria 1	Presence of VUR	Absence of VUR	Total
Positive RBUS	24	57	81
Negative RBUS	15	39	54
Totals	39	96	135
Criteria 2	Presence of VUR	Absence of VUR	Total
Positive RBUS	21	17	38
Negative RBUS	18	79	97
Totals	39	96	135
UET	Presence of VUR	Absence of VUR	Total
Positive RBUS	29	37	66
Negative RBUS	10	59	69
Totals	39	96	135
Any VUR	Criteria 1	Criteria 2	UET
Sensitivity	62%	54%	74%
Specificity	41%	82%	61%
PPV	30%	55%	44%
NPV	72%	81%	86%
LR+	1.05	3.04	1.93
LR-	0.93	0.56	0.42
OR (95% CI)	1.09 (0.51-2.35)	5.42 (2.39-12.30)	4.62 (2.02-10.58)
Criteria 1	Presence of HGVUR	Absence of HGVUR	Total
Positive RBUS	14	67	81
Negative RBUS	2	52	54
Totals	16	119	135
Criteria 2	Presence of HGVUR	Absence of HGVUR	Total
Positive RBUS	16	22	38
Negative RBUS	0	97	97
Totals	16	119	135
UET	Presence of HGVUR	Absence of HGVUR	Total
Positive RBUS	15	51	66
Negative RBUS	1	68	69
Totals	16	119	135
HGVUR	Criteria 1	Criteria 2	UET
Sensitivity	88%	100%	94%
Specificity	44%	82%	57%
PPV	17%	42%	23%
NPV	96%	100%	99%

Criteria 1	Presence of VUR	Absence of VUR	Total
LR+	1.57	5.41	2.19
LR-	0.27	0	0.11
OR (95% CI)	5.43 (1.18-24.97)	143.00 (8.27-2473.74)	20.00 (2.56-156.38)

* Criteria 1: presence of HN SFU grade 3-4 or HU

Criteria 2: presence of at least two of the following: UET; HU; duplication; renal dysmorphia.