Urodynamic Abnormalities in Toilet Trained Children With Primary Vesicoureteral Reflux

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Purpose: We investigated associated urodynamic abnormalities in toilet trained children with vesicoureteral reflux.

Materials and Methods: A total of 298 toilet trained children with primary vesicoureteral reflux underwent urodynamic evaluation. Urodynamic parameters were reviewed and correlated with age, gender, presence of lower urinary tract symptoms and reflux severity.

Results: Symptomatic lower urinary tract symptoms were present in 111 children (37.2%, group 1). Children with lower urinary tract symptoms had significantly decreased severity of vesicoureteral reflux compared to children without these symptoms (187 patients, group 2). The majority of the patients had normal early bladder compliance regardless of presence of lower urinary tract symptoms or reflux grade. On the other hand, decreased late bladder compliance was more common in group 1 vs group 2. Ratio of cystometric bladder capacity to expected bladder capacity was higher in group 2. Detrusor overactivity was observed in 28.5% of the children, and the incidence was significantly higher in group 1 vs group 2, and in mild vs moderate or severe reflux. Dysfunctional voiding from bladder sphincter dyscoordination was seen in 32% of children 2.5 to 4 years old with vesicoureteral reflux and lower urinary tract symptoms, compared to 8% in children 5 to 16 years old.

Conclusions: The presence of lower urinary tract symptoms in children with vesicoureteral reflux correlated well with some urodynamic findings suggestive of overactive bladder and negatively correlated with reflux severity. In contrast, dysfunctional voiding was more common in younger children with reflux and lower urinary tract symptoms. These findings suggest that treatment of voiding dysfunction should be directed toward the specific type of abnormality in children with vesicoureteral reflux.

Key Words: urinary tract, urination disorders, urodynamics, vesico-ureteral reflux

Abbreviations and Acronyms

BC = bladder compliance
CBC = cystometric bladder capacity
DO = detrusor overactivity
DV = dysfunctional voiding
EBC = expected bladder capacity
EMG = electromyogram
LUTS = lower urinary tract symptoms
OAB = overactive bladder
PVR = post-void residual
UDS = urodynamic study
VCUG = voiding cystourethrogram
VUR = vesicoureteral reflux

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While the etiology of primary vesicoureteral reflux is incompetence of a valvular mechanism at the ureterovesical junction, lower urinary tract symptoms may be responsible for development of reflux in children without a congenital abnormality of the ureterovesical junction. It is believed that lower urinary tract symptoms result in increased storage and/or voiding pressures, which in turn cause a spectrum of intravesical anatomical distortions that predispose to reflux. Clinically it is observed that lower urinary tract symptoms may delay spontaneous resolution of reflux, and

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can affect the success of endoscopic and open surgical treatment.[1–3] The reported prevalence of bladder dysfunction in children with vesicoureteral reflux after toilet training varies according to study design. Studies based on urodynamic evaluation have revealed an increased prevalence of lower urinary tract symptoms (38% to 75%) compared to those based on other clinical data (18% to 52%).[4–9] While there seems to be a close relationship between lower urinary tract symptoms and vesicoureteral reflux, specific evidence for this association is lacking and the few published results have been conflicting. In addition, it is hard to find published reports that contain detailed urodynamic data regarding presence of lower urinary tract symptoms and different vesicoureteral reflux grades in toilet trained children. We investigated the relationship between lower urinary tract symptoms and vesicoureteral reflux in toilet trained children based on urodynamic data.

MATERIALS AND METHODS

As a standard of practice, 347 toilet trained children 2.5 to 16 years old who had been diagnosed with primary VUR on VCUG performed for evaluation of a febrile urinary tract infection underwent followup evaluation with a combined radionuclide cystogram and urodynamic study between February 1998 and February 2008. One inclusion criterion was completion of toilet training, so that children who were not toilet trained were excluded from the study even if they were old enough to participate. Initial diagnosis of VUR was made with VCUG for boys and radionuclide cystogram for girls, and the followup study after 1 year included radionuclide cystogram and conventional UDS. However, once children were identified as normal on UDS, there was no need to repeat UDS thereafter.

Patient demographics and clinical data, including severity of VUR, presence of LUTS, 3-day voiding diary and urodynamic data, were obtained from an institutional review board approved urodynamic database prospectively maintained at our hospital. Children with other lower urinary tract pathology that could cause secondary reflux, ie posterior urethral valves, neurogenic bladder, prune belly syndrome, megacystis-megaureter complex or spinal cord anomalies, were excluded. A complete data set was obtained in 68 males and 230 females with reflux who met inclusion criteria. LUTS were determined based on history taking, repeated observation of voiding pattern and voiding diary. LUTS were categorized as storage symptoms (daytime incontinence, frequency, urgency), voiding symptoms (hesitancy, weak stream, intermittency, straining to void) and other symptoms (post-void dribble, holding maneuvers). Bowel dysfunction was assessed as well and diagnosed with a bowel elimination questionnaire containing bowel habits, including number of bowel movements weekly, associated pain or straining, and presence and frequency of fecal soiling. Type of stool was reported based on Bristol Stool Form Scale.[10] Physical examination of the abdomen was routinely done for fecal mass or distention.

For analysis children with LUTS were designated as group 1 and those without LUTS as group 2. VUR grade was classified into 3 categories, based on radionuclide cystogram findings, as mild (grade I on VCUG), moderate (grades II and III) and severe (IV and V). When VUR was bilateral, the higher grade was used for grade classification. Urodynamic parameters obtained included cystometric bladder capacity, early (first half of filling phase) and late (second half of filling phase) bladder compliance, presence of detrusor overactivity, detrusor pressure at cystometric bladder capacity, maximum detrusor pressure during voiding and PVR volume. DO was defined as involuntary detrusor contractions during the filling phase with a detrusor pressure increase of 15 cm H_2O or more above baseline before reaching age related EBC, which was calculated via the formula, [30 + (age in years × 30)] in ml.[11] To compare CBC in children of different ages, CBC was expressed as a ratio to age related EBC. DV was diagnosed when there was a significant contraction of the external urethral sphincter observed during voiding and detected by uroflow curves as showing a staccato or interrupted pattern repeatedly, or by cystometrogram as impaired silencing of EMG during the voiding phase. Statistical analysis was performed using Student's t test, one-way ANOVA and chi-square cross-tabulation analysis, with $p < 0.05$ being significant (SAS®, version 9.2).

RESULTS

Mean ± SD patient age at urodynamic evaluation was 6.9 ± 3.9 years (range 2.5 to 16). LUTS were present at evaluation in 111 patients (37.2%) with a male-to-female ratio of 1:4.8. Overall rates of mild, moderate and severe VUR were 19.4% (58 patients), 42.3% (126) and 38.3% (114), respectively. Irritative symptoms were reported in 89 patients (80.2%) and obstructive symptoms in 37 (33.3%). Incontinence was the most common single presenting symptom (78 patients, 70.3%). Urgency was reported in 61 patients (55%) in group 1, of whom 52 (85%) had various degrees of incontinence.

A history of bowel dysfunction was present in 126 children (42.3%), of whom 89 (70.6%) had LUTS. Figure 1 illustrates the distribution of reflux grade in children with and without LUTS at UDS. Interestingly children without LUTS demonstrated a higher prevalence of moderate or severe VUR than those with LUTS (83.2% vs 69%, $p = 0.025$). Otherwise, there were no statistically significant differences between groups 1 and 2 regarding age or gender. A trend was identified toward severe grade of reflux in patients without LUTS ($p = 0.55$ and $p = 0.21$).

On urodynamic evaluation 282 children (94.6%) had a normal early BC regardless of LUTS or reflux grade. On the other hand, decreased late BC was more common in group 1 than group 2 (39 vs 41 patients, 35.1% vs 21.9%, $p = 0.041$). Figure 2 illustrates correlation of specific urodynamic findings

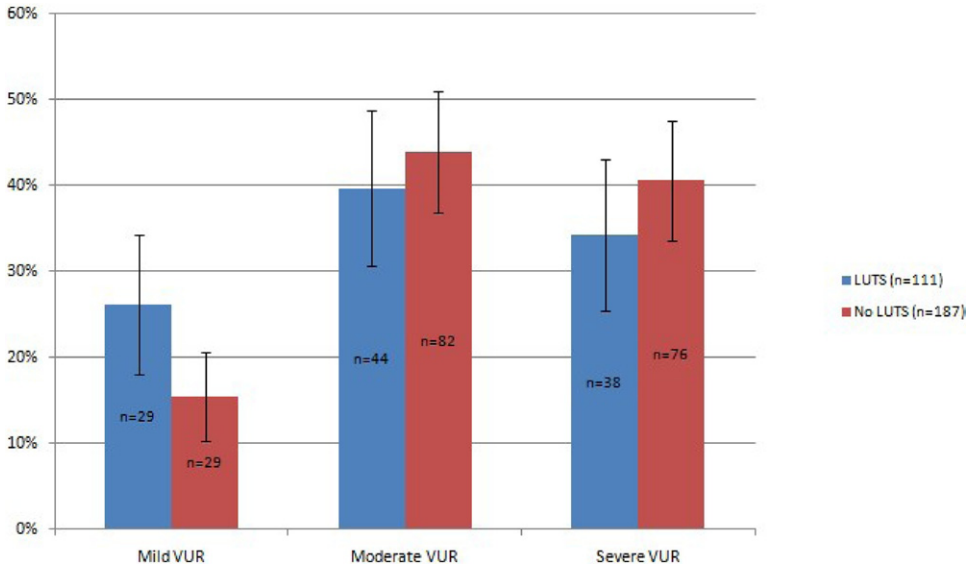

Figure 1. Distribution of VUR severity in children with and without LUTS (95% CI)

with specific voiding symptoms. DO was observed in 85 patients (28.5%) and the prevalence was significantly higher in group 1 than group 2 (48 vs 37 patients, 43.2% vs 19.8%, p = 0.012), and in mild or severe vs moderate reflux (tables 1 and 2). Of 61 children with urgency 38 (62%) exhibited DO. Incontinence was reported in 78 children, of whom 44 (56%) had DO.

Ratio of CBC to EBC was higher in group 2 (1.15 vs 1.34, p = 0.032). A total of 57 children had a staccato uroflow pattern, of whom 26 (46%) displayed evidence of dysfunctional voiding on UDS. DV was observed in 58 children (19.4%) overall, including 17 (15.3%) in group 1 and 41 (21.9%) in group 2. DV was noted more frequently in younger children (2.5 to 4 years) with LUTS than in older children (older than 4) with LUTS (11 of 34 vs 6 of 77 patients, 32% vs 8%, p <0.05). Two girls and 1 boy had DO plus DV.

Other urodynamic factors did not have any significant correlation with VUR grade or presence of LUTS. Figure 3 represents a histogram of DO/DV per year class coupled with reflux grade and composition of gender.

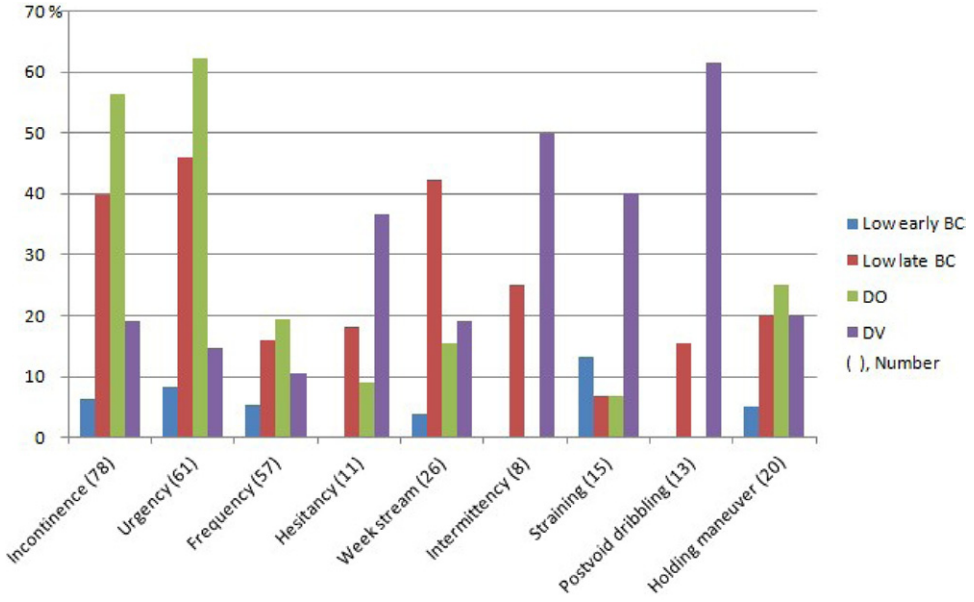

Figure 2. Correlation of voiding symptoms with urodynamic findings

Table 1. *Urodynamic results based on presence or absence of LUTS*

	Pts With LUTS	Pts Without LUTS	Totals/Av
No. low BC (%):*			
Early	7 (6.3)	9 (4.8)	16 (5.4)
Late†	39 (35.1)	41 (21.9)	80 (26.8)
Mean ± SD CBC/EBC†	1.15 ± 0.47	1.34 ± 0.59	1.27 ± 0.31
Mean ± SD max detrusor pressure‡	47.14 ± 14.20	45.21 ± 17.39	45.92 ± 11.56
Mean ± SD PVR/CBC§	0.15 ± 0.027	0.19 ± 0.036	0.17 ± 0.018
No. DO (%)†	48 (43.2)	37 (19.8)	85 (28.5)
No. DV (%)	17 (15.3)	41 (21.9)	58 (19.4)

* Normal values greater than 10 ml/cm H_2O.[20]

† $p < 0.05$.

‡ Median values 100 cm H_2O in male infants and 70 cm H_2O in female infants, 70 cm H_2O in 1 to 3-year-old males and 60 cm H_2O in 1 to 3-year-old females, and similar to adults in children older than 7 years.[20]

§ Median values 4 to 5 ml up to age 2 years, 0 ml at 3 years and older.[20]

DISCUSSION

We observed that 37% of toilet trained children with VUR had signs or symptoms suggestive of lower urinary tract dysfunction, similar to the rate of 46% reported by Koff et al.[4] Incontinence was the most common lower urinary tract symptom, with irritative and obstructive symptoms being less problematic. Recent concepts regarding LUTS in children with reflux suggest that the condition is not a single entity, but rather one that can be divided into 2 distinct subtypes, ie DV and OAB.[1] It is generally perceived that LUTS in children with reflux result primarily from DV. This is only the case when VUR is associated with dysfunction of the external urethral sphincter during the voiding phase, which is characterized by increased activity in the pelvic floor, resulting in a staccato or interrupted voiding pattern on repeated uroflow measurements.[11] In contrast, OAB usually results from DO during filling, with the subjective hallmark symptom of urgency with or without incontinence.

In this study the rates of DO and DV in toilet trained children with VUR were 28.5% and 19.4%, respectively. We observed that children with reflux and LUTS had evidence of smaller cystometric bladder capacity, lower late bladder compliance and increased incidence of DO, all of which are urodynamic characteristics of OAB. However, DV was observed more frequently in younger children with VUR and LUTS. Based on this distinction in the subtypes of voiding dysfunction, reanalysis of previously reported studies indicates that the prevalence of DO ranges from 8% to 38%, and DV from 6% to 27% in children with VUR, with a higher incidence of DV in the younger cohort and of DO in older children.[4,6,7,12] This observation is in agreement with studies of children with high grade VUR diagnosed during infancy, revealing the bladder dysfunction is primarily characterized by dyscoordination of the sphincter with the bladder during voiding, producing a larger than expected capacity bladder and incomplete emptying.[13,14] Together, these findings suggest that the type of voiding dysfunction in children with VUR is principally DV in infants and younger children, and DO in older children. The question of whether children with VUR and voiding dysfunction exhibit DV first and then progress to DO remains unanswered and can only be solved by longitudinal urodynamic studies.

More children without (21.9%) than with (15.3%) LUTS had DV in this study, although the difference was not significant. Considering that most children with true DV present with urgency and wetting, this finding suggests that DV may involve a spectrum of clinical presentations. However, the only concern in accepting this finding would be the retrospective character of the study and the multiple physicians involved in seeing the subjects, which could represent a potential limitation in obtaining complete patient histories.

Although DO and DV are often combined (we encountered 3 cases in the present study) and they are sometimes difficult to differentiate, these 2 subtypes of LUTS should be distinguished because their treat-

Table 2. *Urodynamic results based on VUR grade*

	Mild VUR	Moderate VUR	Severe VUR	Totals/Av
No. low BC (%):*				
Early	3 (5.2)	4 (3.2)	9 (7.9)	16 (5.4)
Late	13 (22.4)	35 (27.8)	32 (28.1)	80 (26.8)
Mean ± SD CBC/EBC	1.31 ± 0.44	1.25 ± 0.51	1.27 ± 0.56	1.27 ± 0.31
Mean ± SD max detrusor pressure†	48.41 ± 30.83	46.74 ± 23.58	43.83 ± 24.82	45.92 ± 11.56
Mean ± SD PVR/CBC‡	0.16 ± 0.039	0.16 ± 0.051	0.20 ± 0.033	0.17 ± 0.018
No. DO (%)§	23 (39.7)	26 (20.6)	36 (31.6)	85 (28.5)
No. DV (%)	9 (15.5)	23 (18.3)	26 (22.8)	58 (19.4)

* Normal values greater than 10 ml/cm H_2O.[20]

† Median values 100 cm H_2O in male infants and 70 cm H_2O in female infants, 70 cm H_2O in 1 to 3-year-old males and 60 cm H_2O in 1 to 3-year-old females, and similar to adults in children older than 7 years.[20]

‡ Median values 4 to 5 ml up to age 2 years, 0 ml at 3 years and older.[20]

§ $p < 0.05$.

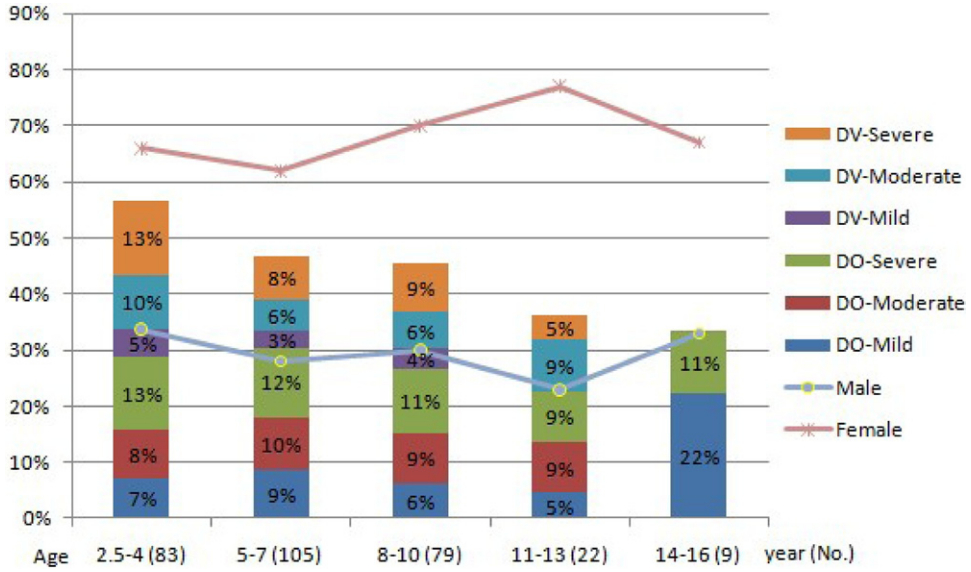

Figure 3. Histogram of DO/DV per year class coupled with reflux grade and composition of gender

ments differ. Anticholinergic therapy may be beneficial in patients with VUR and DO,[15] whereas biofeedback and voiding improvement programs such as timed voiding may be efficacious in those with VUR and DV.[16] From 1980 through the 1990s OAB was suggested to have a major role in association with VUR and its treatment to influence positively the resolution of VUR.[5,17,18] Later, LUTS due to DV was reported to have a negative influence on VUR resolution, while its treatment positively influenced resolution.[4,8,16,19] Our findings support treatment for LUTS in children with VUR based on the etiology of LUTS.

We also observed that children with LUTS had lower grades of reflux compared to those without LUTS. This finding suggests that LUTS may result in development of mild grades of reflux, while higher grades of VUR may be due to an inherent anatomical abnormality of the ureterovesical junction. We also observed that DO was correlated with mild and severe reflux, while DV tended to be associated with severe reflux only. Due to our small numbers, it was not possible to perform multivariate analysis to assess whether these correlations were dependent on factors such as age, gender and LUTS. Studies involving a larger number of children will be required to establish a correlation between the etiology of LUTS and the severity of VUR.

There are several limitations to our study. It is retrospective in character with multiple physicians involved in seeing subjects. Also, the clinical diagnosis of lower urinary tract dysfunction might often be difficult, especially in milder cases, which could result in misclassification of children and potentially alter our results. Additionally we could not include the diagnosis of primary bladder neck dysfunction, which has been known as one of the voiding dysfunctions associated with VUR and is easily detected with noninvasive uroflow/EMG or video UDS. Finally, we did not correlate voiding dysfunction with VUR resolution. The majority of children did not have sufficient followup to determine resolution. Larger numbers of children with longer followup will be required to determine whether treatment of a specific voiding dysfunction will improve the rate of VUR resolution.

CONCLUSIONS

This study shows extensive details of urodynamic findings in toilet trained children with various degrees of VUR and specific voiding dysfunction. It suggests a more complex relationship between voiding dysfunction and VUR than previously described. Based on this study, DO is more likely to appear in older children, while DV is more likely to occur in younger children. Irritative voiding symptoms, including incontinence, reflect DO rather than DV in toilet trained children with VUR. However, it seems that prediction of voiding dysfunction based on voiding symptoms and reflux grades could be misleading. Consequently the therapeutic approach to voiding dysfunction in toilet trained children with VUR should be individualized and accordingly directed toward the specific subtype noted.

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EDITORIAL COMMENT

The relationship between nonneurogenic voiding disorders (ie detrusor overactivity and dysfunctional voiding) and VUR in children, the positive effect their treatment has on reflux resolution, and the likelihood of surgical failure if not identified and treated beforehand have been well documented in the literature. However, despite broad acknowledgement of these concepts, there still seems to be a sizable number of children with VUR in whom the possibility of an associated underlying bladder/voiding abnormality goes unconsidered unless linked with a history of more classic disorders such as spinal dysraphism or posterior urethral valves. While this omission is more likely to occur when nonurological clinicians are treating the child with reflux, it is by no means exclusive to them. A possible explanation for this situation, at least based on my experience, is that after a child has been labeled as having primary reflux there is a perception that there is no need to investigate the bladder further, and that even if LUTS are present, they are often ascribed to the irritative effects of infection or the neurological immaturity of the younger child.

What the authors have done is to include a formal urodynamic evaluation in the assessment and followup of a large group of toilet trained children diagnosed with primary VUR. Interestingly they identified a sizable number who in fact had urodynamically documented abnormalities of storage (DO) and/or voiding (DV) that at least could be fueling the reflux if not arguably being its source. These findings were noted in the group of children with associated LUTS as well as those reported to be asymptomatic. As expected, children with LUTS had higher incidences of DO, impaired compliance and smaller capacities compared to the asymptomatic group. There were also several findings that were somewhat counterintuitive. Low grade VUR was more common in the LUTS group with DO, while DV was noted more frequently in the asymptomatic group (21.9% vs 15.3%). A 20% incidence of DO was also noted in the asymptomatic group.

In contradistinction, in a recent study where a similar number of children (albeit studied specifically for LUTS, not reflux) were evaluated with videourodynamics VUR, particularly moderate and high grade disease, had a much stronger association with DO and DV.[1] All of the children diagnosed with DV were extremely symptomatic and 90% also had documented DO during filling.

Although primary bladder neck dysfunction was not assessed in this current report, another recently published study that included 650 children diagnosed with primary VUR and subsequently evalu-

ated with videourodynamics found underlying primary bladder neck dysfunction in nearly 10%.[2] With alpha-blocker therapy VUR improved or resolved in the majority of patients.

One may debate whether many of these children actually had secondary rather than primary reflux, as the authors suggest, or whether dysfunctional voiding is a valid diagnosis if the child has no associated LUTS, or even what the true relationship is between reflux grade and urodynamic abnormalities. What is not in dispute is the take home message of the authors, which is clear and on target, namely that children with reflux are best served when associated abnormalities of storage and/or voiding are carefully screened for and, if present, therapy is tailored to address those abnormalities. One must be especially vigilant when a child presents with reflux after toilet training, particularly if there are associated LUTS and/or bowel complaints. Screening with a noninvasive uroflow study, performed with simultaneous pelvic floor EMG, can be useful in identifying underlying voiding disorders in these children.

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