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Original Article: Clinical Investigation

Can we predict vesicoureteral reflux resolution in patients with non-neurogenic lower urinary tract dysfunction?

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Abbreviations & Acronyms
AUA = American Urological Association
BWT = bladder wall thickness
DUD = detrusor underutilization disorder
DV = dysfunctional voiding
DVISS = Dysfunctional Voiding and Incontinence Symptom Score
EBC = expected bladder capacity
EMG = electromyography
IDOD = idiopathic detrusor overactivity
IRSCGS = International Reflux Study Committee Grading System
LUTS = lower urinary tract symptoms
NNLUTD = non-neurogenic lower urinary tract dysfunction
PBND = primary bladder neck dysfunction
PVR = post-void residual urine
UF = uroflowmetry
USG = ultrasonography
UTI = urinary tract infection
VCU = voiding cystourethrography
VUDS = videourodynamics
VUR = vesicoureteral reflux

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Objective: To analyze factors influencing reflux resolution in patients with the coexistence of non-neurogenic lower urinary tract dysfunction and vesicoureteral reflux.
Methods: The data of 153 children who were diagnosed with vesicoureteral reflux and accompanying non-neurogenic lower urinary tract dysfunction between 2010 and 2015 were retrospectively evaluated. Patients with neurogenic and anatomical malformations, monosymptomatic nocturnal enuresis, previous history of vesicoureteral reflux surgery, irregular and/or incomplete follow-up data were excluded. After exclusion of 55 patients, 98 patients were enrolled in this study. Patients were divided into two groups according to the presence of spontaneous vesicoureteral reflux resolution during the follow-up period. Group 1 consisted of 54 children with spontaneous vesicoureteral reflux resolution, whereas group 2 included 44 children without resolution. Medical history, physical examination, urinalysis, uroflowmetry combined with electromyography, ultrasonography, as well as the Dysfunctional Voiding and Incontinence Symptom Score questionnaire were also evaluated.
Results: The mean age at presentation was 7.57 ± 0.23 years (range 5–13 years), and the mean follow-up period was 28.3 months. Significant differences were noted between the two groups in terms of dysfunctional voiding and incontinence symptom score, bladder wall thickness, and the post-void residual urine volumes. In addition, lower urinary tract symptoms, namely frequency, urgency and daytime incontinence, were found to be higher in group 2. In multivariate analysis, post-void residual urine volume and Dysfunctional Voiding and Incontinence Symptom Score were found to affect reflux resolution rates ($P = 0.002$, $P = 0.002$, respectively).
Conclusions: The absence of significant post-void residual urine volume, and a low Dysfunctional Voiding and Incontinence Symptom Score increase the likelihood of spontaneous resolution rates of vesicoureteral reflux in children with non-neurogenic lower urinary tract dysfunction.

Key words: children, non-neurogenic lower urinary tract dysfunction, post-void residual urine, reflux resolution, vesicoureteral reflux.

Introduction

NNLUTD is a common condition, comprising 30–40% of the patients admitted to pediatric urology clinics.[1,2] NNLUTD can either exist alone or coexists with incontinence, UTI or VUR.[3] VUR and NNLUTD coexistence occurs especially in children presenting with febrile UTI, within the period after toilet training.[4] Despite the fact that the natural course of these two conditions and interaction between them has not been clearly shown yet, it has been shown that spontaneous VUR resolution and the success rate of interventional treatment aimed to correct VUR is relatively low in the case of VUR and NNLUTD coexistence.[5–7]

In the present study, we aimed to show the factors influencing spontaneous VUR resolution in children with the coexistence of NNLUTD and VUR.

Methods

After we obtained the approval from the local ethics committee, the medical records of 153 patients who were diagnosed with VUR and accompanying NNLUTD between 2010 and 2015 were retrospectively evaluated. Patients with neurogenic and anatomical malformations, monosymptomatic nocturnal enuresis, previous history of VUR surgery, irregular and/or incomplete follow-up data were excluded from the study. After the exclusion of 55 patients, 98 patients were enrolled in the present study.

For each patient, the medical recordings of physical examination, medical history, UF combined with EMG and USG, as well as DVISS, were also evaluated.

DVISS, which includes 10 questions, is a validated questionnaire and is used to assess the severity of DV habits in children.[1] We use the modified DVISS questionnaire, which is validated by Akbal *et al.*[8] This questionnaire was composed of 13 questions regarding daytime symptoms, nighttime symptoms, voiding habits, bowel habits and one quality of life question at the end. The total score was determined to range from 0 to 35. It is reported that patients with a score of ≥8.5 had voiding abnormalities, with a sensitivity of 90% and a specificity of 90%.[8]

All children with febrile UTI were assessed for VUR with VCU. VUR grades were labeled on the basis of radiological findings using the IRSCGS.[9]

Upper urinary tract and BWT was evaluated by using USG. The distance between two hyperechogenic lines of the distended bladder wall was measured to calculate the BWT.[10] The BWT value was considered as the average of the three BWT values that were obtained from three different regions of the bladder. The presence of adequate volume before voiding was also confirmed by USG.

UF/EMG was carried out and analyzed in all patients with a distended bladder by a single experienced clinician (HT). EMG patch electrodes were attached at the margin of the external anal sphincter at the 3 o'clock and 9 o'clock positions. The presence or absence of pelvic floor activity during voiding was recorded. After the UF/EMG test was completed, USG was carried out to measure PVR volume. All patients underwent USG evaluation twice in a single day and the higher measurement was considered as the PVR volume.

PVR volume >20 mL or >10% of EBC and PVR volume >20 mL or >15% of EBC were considered as significant PVR for patients aged 4–6 years and >6 years, respectively.[11] The EBC was estimated by using the Koff's formula [(age in years + 2) × 30].[12]

We used certain UF/EMG features and clinical history to assign patients one of the four different lower urinary tract conditions, which was previously defined by using either urodynamic studies or UF/EMG tests.[7] According to symptoms and UF/EMG recordings, we categorized our patients into one of the following four NNLUTD subgroups: 1-DV: active pelvic floor during voiding (active EMG) associated with straining, hesitancy or interrupted voiding and urinary incontinence; 2-IDOD: inactive pelvic floor during voiding (inactive EMG), with predominant symptoms of urgency, frequent voiding and urge incontinence with normal or low bladder capacity; 3-DUD: inactive pelvic floor during voiding (inactive EMG), with high bladder capacity (>125% of EBC) associated with normal voiding pattern as a result of habitual delaying urination; and 4-PBND: inactive pelvic floor during voiding (inactive EMG), with insufficient urine emptying due to late or incomplete opening of the bladder neck associated with the predominance of hesitancy.

All patients were given standard voiding urotherapy, including voiding training, behavioral modifications, voiding therapy and bowel management. In the DV group, anticholinergic therapy was added to the standard urotherapy if the patient had the symptoms of bladder overactivity, such as urgency and urge incontinence. Anticholinergic therapy was also given to patients with IDOD. Within the context of urotherapy, the patients with DUD were strongly advised to void timely. All patients were given antimicrobial prophylaxis. In our study group, PBND was not detected in any patients.

Urinalysis, urine culture and antibiogram, DVISS, UF/EMG, and USG were repeated for all patients 3 months after the initiation of treatment. Different from the other tests, which were repeated every 3 months, VCU was repeated every 6 months. After 6 months of VUR resolution, VCU was also repeated to confirm resolution.

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) for windows (version 18.0; SPSS, Chicago, IL, USA) software. The categorical variables were described by frequencies and percentages, and the continuous variables were presented with means and standard deviations. The means were compared by *t*-test. The χ^2-test and Fisher's exact tests were used for categorical variables. To determine the variables associated with prognosis, regression analysis was carried out. Sex, BWT, PVR, DVISS score, VUR grade and LUTS condition type were included in the regression analysis. A *P*-value <0.05 was considered as statistically significant.

Results

We analyzed findings of 49 boys and 49 girls with a mean age of 7.57 ± 0.23 years (range 5–13 years). Patients were divided into two groups according to the presence of VUR resolution during the follow-up period. Group 1 consisted of 54 children with spontaneous VUR resolution, while group 2 included 44 children without resolution. Demographic patient data, duration of follow up, PVR, DVISS, BWT, VUR grade and NNLUTD subgroups are shown in Table 1.

A significant difference was detected between the two groups regarding PVR, DVISS, BWT and NNLUTD condition ($P = 0.008$, $P = 0.001$, $P = 0.001$ and $P = 0.003$, respectively). Grade 1 and grade 2 reflux were observed at higher rates in group 1, whereas group 2 was associated with patients with a higher grade reflux, such as grade 3 and 4. Grade 5 reflux and bilateral reflux were not present in any patient. Nevertheless, VUR grade was not statistically different between the two groups ($P = 0.06$). The distribution of VUR grades with respect to the NNLUTD subgroups of the patients is shown in Table 2. DV was observed to be higher in patients with grade 3 reflux, whereas IDOD was found to

Table 1 Comparison of the variables between two groups

Variables	Total (*n* = 98)	Group 1 (resolution) (*n* = 54; 55.1%)	Group 2 (no resolution) (*n* = 44; 44.9%)	*P*
Age, years (mean ± SD)	7.57 ± 0.23	7.72 ± 2.46	7.38 ± 2.19	0.483
Sex, *n* (%)				
Male	49 (50.0)	24 (44.4)	25 (56.8)	0.310
Female	49 (50.0)	30 (55.6)	19 (43.2)	
Follow up (months) (mean ± SD)	28.3 ± 15.4	21.68 ± 6.8	20.1 ± 5.7	0.236
PVR				
Significant	50 (51.0)	21 (38.9)	29 (65.9)	0.008
Non-significant	48 (49.0)	33 (61.1)	15 (34.1)	
DVISS (mean ± SD)	16.3 ± 0.68	13.8 ± 5.63	19.09 ± 7.64	0.001
BWT, mm (mean ± SD)	1.40 ± 0.48	1.40 ± 0.51	1.93 ± 1.37	0.001
VUR, *n* (%)				
Grade 1	14 (14.3)	10 (18.5)	4 (9.1)	0.060
Grade 2	32 (32.7)	22 (40.7)	10 (22.7)	
Grade 3	43 (43.9)	18 (33.3)	25 (56.8)	
Grade 4	9 (9.1)	4 (7.4)	5 (11.4)	
Grade 5	0	0	0	
NNLUTD, *n* (%)				
DV	52 (53.1)	21 (38.9)	31 (70.5)	0.003
IDOD	38 (38.7)	29 (53.7)	9 (20.5)	
DUD	8 (8.1)	4 (7.4)	4 (9.0)	
PBND	0	0	0	

Table 2 Distribution of VUR grades with respect to NNLUTD subgroups

NNLUTD subgroups	VUR-G1 *n* (%)	VUR-G2 *n* (%)	VUR-G3 *n* (%)	VUR-G4 *n* (%)	VUR-G5 *n* (%)	Total *n* (%)
DV	5 (5.1)	4 (4.1)	35 (35.7)	8 (8.1)	0	52 (53.1)
IDOD	1 (1.0)	28 (28.6)	8 (8.1)	1 (1.0)	0	38 (38.8)
DUD	8 (8.1)	0	0	0	0	8 (8.1)
PBND	0	0	0	0	0	0
Total	14 (14.3)	32 (32.7)	43 (43.9)	9 (9.1)	0	

Table 3 Comparison of LUTS in both groups

	Group 1 (resolution) *n* (%)	Group 2 (no resolution) *n* (%)	*P*
Frequency	12 (22.2)	20 (45.4)	0.010
Urgency	18 (33.3)	25 (56.8)	0.010
Daytime incontinence	4 (7.4)	18 (40.9)	0.020
Constipation	14 (25.9)	13 (29.5)	0.847

Table 4 Logistic regression analysis data of effective factors in VUR resolution

Variables	OR (95% CI)	*P*
BWT	0.73 (0.768–5.695)	0.149
VUR grade	−0.45 (0.115–3.924)	0.598
NNLUTD	−1.08 (0.337–0.094)	0.094
PVR	1.79 (1.982–18.237)	0.002
DVISS	1.92 (2.205–22.200)	0.002
Sex	−1.14 (0.060–0.988)	0.080

be higher in patients with grade 2 reflux. The LUTS of the patients in both groups are shown in Table 3. The comparison between two groups showed that patients in group 2 had significantly higher LUTS of frequency, urgency and daytime incontinence.

Subsequently, a multivariate logistic regression analysis was carried out in order to evaluate the strength of predictive factors (Table 4). BWT, VUR grade, NNLUTD subgroups, PVR, DVISS and sex were analyzed, and PVR and DVISS were found to be influential factors in VUR resolution ($P = 0.002$, $P = 0.002$, respectively). The cut-off values of DVISS and BWT were observed as 16.2 and 1.64 mm, respectively.

Discussion

There is a close relationship between VUR and NNLUTD.[13] The prevalence of bladder dysfunction ranged between 18 and 75% in patients with VUR. In contrast, the prevalence of VUR was shown to be 14–47% in patients with NNLUTD.[14] According to the 2010 AUA guidelines on primary VUR, spontaneous VUR resolution was reported to be 31% in the case of coexisting NNLUTD and VUR, whereas this rate increased to 61% in those without coexistence.[5]

VUDS is the gold standard in the diagnosis of NNLUTD. Anatomical abnormalities, detrusor pressure during the filling and voiding phases, bladder neck, and external sphincter activity can be assessed in real-time by using VUDS.[7] Some of the disadvantages of this method, such as invasive nature, availability, cost and potential radiation exposure, limit its use in practice. In addition, some authors believed that VUDS does not generally change the management and treatment of NNLUTD.[7,15]

In contrast, UF/EMG is a non-invasive, practical and easily applied test that allows the measurement of pelvic floor electrical activity during voiding, which is a surrogate for the external urethral sphincter.[7] The superiority of the UF/EMG combination was reported over UF alone or a conventional urodynamic study.[15] It helps to identify the different types of NNLUTD and improves diagnostic accuracy.

With the help of presenting LUTS, UF/EMG patterns were categorized into one of the four urodynamically-defined patterns, which were described previously.[7,16]

USG, which is a non-invasive, fast and inexpensive method, plays a key role in the assessment of pediatric patients with NNLUTD.[17,18] Both neurogenic and non-neurogenic voiding dysfunction might lead to hypertrophy of the bladder wall and increased intravesical pressure.[19] Increased deposition of collagen in the bladder wall leads to bladder wall hypertrophy by thickening of the detrusor.[20] Although a definitive cut-off value was not specified, BWT was found to be significantly higher in children with DV compared with

children with a normal voiding pattern.[18] Furthermore, patients with frequent UTI and urodynamically proven overactive bladder were reported to have lower bladder capacity and a thicker bladder wall.[21]

When we evaluated the influence of BWT on reflux resolution, a significant difference was found between the two groups ($P = 0.001$). Nevertheless, this difference was not observed in multivariate analysis.

PVR measurement and PVR cut-off values vary significantly among children.[11] PVR appears as an important component in children with NNLUTD. The present study showed significantly different PVR amounts between the patients with and without VUR resolution both in univariate and multivariate analysis ($P = 0.008$ and $P = 0.002$, respectively). There is no agreement on the cut-off value to consider the PVR as significantly increased. Nevertheless, we used the reference values described by International Children's Continence Society for PVR to define the increased amount.[11] In their study using the same references for increased PVR, Beksac *et al.* claimed that increased PVR is the most significant non-invasive diagnostic test to predict the treatment outcome in children with NNLUTD.[22]

NNLUTD is considered as one of the several variables that influences various pediatric urological conditions, including the presence and persistence of VUR.[23] The DVISS is a validated questionnaire that assesses the severity of DV habits, daytime symptoms, night-time symptoms and bowel habits in children.[1,8] In this context, the DVISS questionnaire can be thought of as a tool predicting reflux resolution children with coexisting NNLUTD and VUR. Upadhyay *et al.* reported that a significant decrease in the DVISS predicts the future resolution of VUR accompanied by NNLUTD with expectant management.[23] Similarly, we observed DVISS >16.2 as a negative factor in terms of spontaneous reflux resolution.

According to the initial AUA guidelines for VUR management, VUR grade, age and laterality were thought to be primary determinants for spontaneous reflux resolution.[24] Nevertheless, recent studies showed that reflux resolution is a more sophisticated process than previously thought, and is influenced by voiding dysfunction, coexisting anomalies, sex, timing of reflux and the mode of presentation.[25,26]

Regarding the relationship with VUR severity and NNLUTD conditions, we observed that DV was more common in patients with grade 3 reflux, whereas IDOD was observed at a higher rate in the grade 2 reflux group. In a Swedish study, grade 4 reflux was detected at a high rate (59%) in patients with DV, whereas grade 3 reflux was observed in 87% of patients with IDOD.[27]

Although VUR grade distribution showed differences among NNLUTD subgroups, we were not able to determine VUR grade as a predictive factor for reflux resolution in patients with NNLUTD in multivariate analysis ($P = 0.598$). This finding might be attributed to fact that of the 98 patients evaluated, grade 5 reflux was not present in any patient, and just eight patients had grade 4 reflux.

Studies evaluating the effect of NNLUTD subgroups on reflux resolution gave conflicting results.[4,27] Similar to a Swedish study, we obtained higher rates of reflux resolution in patients with accompanying IDOD, when compared with DV (53.7% and 38.9%, respectively).[27] In contrast, Fast *et al.* reported a higher spontaneous reflux resolution rate in patients with DV than IDOD (57% and 35%, respectively).[4]

We observed that NNLUTD subgroup was not found to be a predictive factor for VUR resolution in the multivariate analysis ($P = 0.094$). This might be related the fact that of the 98 patients evaluated, PBND was not present in any patient, and DUD was found in just eight patients.

The present study had several limitations that need to be considered in interpreting the findings. First, the data were collected retrospectively, which can be considered as an inherent limitation. Second, the limited number of patients enrolled in the study precluded interpretation of the results specifically related with the NNLUTD subgroups. Finally, effect of laterality as a predictive factor of VUR resolution could not evaluated because of the lack of any patient presenting with bilateral reflux.

In conclusion, the specific nature of the interaction between spontaneous VUR resolution and NNLUTD requires further investigation. The absence of significant PVR and low DVISS were found to be the factors increasing the spontaneous VUR resolution in children with accompanying NNLUTD. Large-scale, prospective studies are required to support the findings of the present study.

Conflict of interest

None declared.

References

1 Farhat W, Bagli D, Capolicchio G *et al.* The dysfunctional voiding scoring system: quantative standardization of dysfunctional voiding symptoms in children. *J. Urol.* 2000; **164**: 1011–5.

2 Rushton HG. Wetting and functional voiding disorders. *Urol. Clin. North Am.* 1995; **22**: 75–93.

3 Ballek NK, McKenna PH. Lower urinary tract dysfunction in childhood. *Urol. Clin. North Am.* 2010; **37**: 215–28.

4 Fast AM, Nees SN, Van Batavia JP, Comnbs AJ, Glassberg KI. Outcomes of targeted treatment for vesicoureteral reflux in children nonneurogenic lower urinary tract dysfunction. *J. Urol.* 2013; **190**: 1028–32.

5 Skoog SJ, Peters CA, Arant BS Jr *et al.* Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. *J. Urol.* 2010; **184**: 1145–51.

6 Sjöström S, Sillén U, Jodal U, Sameby L, Sixt R, Stokland E. Predictive factors for resolution of congenital high grade vesicoureteral reflux in infants: results of univariate and multivariate analyses. *J. Urol.* 2010; **183**: 1177–84.

7 Van Batavia JP, Combs AJ, Hyun G, Bayer A, Medina-Kreppein D, Schlussel RN. Simplifying the diagnosis of 4 common voiding conditions using uroflow/electromyography, electromyography lag time and voiding history. *J. Urol.* 2011; **186**: 1721–6.

8 Akbal C, Genç Y, Burgu B, Ozden E, Tekgül S. Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. *J. Urol.* 2005; **173**: 969–73.

9 Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International Reflux Study in Children. International system of radiographic grading of vesicoureteric reflux. *Pediatr. Radiol.* 1985; **15**: 105–9.

10 Müller L, Bergstrom T, Hellstrom M, Svensson E, Jacobsson B. Standardized ultrasound method for assessing detrussor muscle thickness in children. *J. Urol.* 2000; **164**: 134–8.

11 Austin PF, Bauer SB, Bower W *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. *J. Urol.* 2014; **191**: 1863–5.

12 Koff SA. Estimating bladder capacity in children. *Urology* 1983; **21**: 248.
13 Van Batavia JP, Nees SN, Fast AM, Combs AJ, Glassberg KI. Outcomes of vesicoureteral reflux in children with non-neurogenic lower urinary tract dysfunction treated with dextranomer/hyaluronic acid copolymer (Deflux). *J. Pediatr. Urol.* 2014; **10**: 482–7.
14 Sillén U. Bladder dysfunction and vesicoureteral reflux. *Adv. Urol.* 2008; **200**: 1–8.
15 Babu R, Gopinath V. Role of uroflowmetry with electromyography in the evaluation of children with lower urinary tract dysfunction. *Indian J. Urol.* 2015; **31**: 354–7.
16 Glassberg KI, Combs AJ, Horowitz M. Nonneurogenic voiding disorders in children and adolescents: clinical and videourodynamic findings in 4 specific conditions. *J. Urol.* 2010; **184**: 2123–7.
17 Neveus T, Eggert P, Evans J *et al.* Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. *J. Urol.* 2010; **183**: 441–7.
18 Tangal S, Gökçe Mİ, Özayar A *et al.* Evaluation of a new ultrasound measurement tool for the diagnosis of dysfunctional voiding in pediatric population: full/empty bladder wall thickness ratio. *Urology* 2014; **83**: 1369–72.
19 Oelke M. International Consultation on Incontinence-Research Society (ICI-RS) report on non-invasive urodynamics: the need of standardization of ultrasound bladder and detrusor wall thickness measurements to quantify bladder wall hypertrophy. *Neurourol. Urodyn.* 2010; **29**: 634–9.
20 Levin RM, Haugaard N, O'Connor L *et al.* Obstructive response of human bladder to BPH vs. rabbit bladder response to partial outlet obstruction: a direct comparison. *Neurourol. Urodyn.* 2000; **19**: 609–29.
21 Yeung CK, Sreedhar B, Leung YF, Sit KY. Correlation between ultrasonographic bladder measurements and urodynamic findings in children with recurrent urinary tract infection. *BJU Int.* 2007; **99**: 651–5.
22 Beksac AT, Koni A, Bozaci AC, Dogan HS, Tekgul S. Postvoidal residual urine is the most significant non-invasive diagnostic test to predict the treatment outcome in children with non-neurogenic lower urinary tract dysfunction. *J. Pediatr. Urol.* 2016; **12**: 215.e1–8.
23 Upadhyay J, Bolduc S, Bagli DJ, McLorie GA, Khoury AE, Farhat W. Use of the dysfunctional voiding symptom score to predict resolution of vesicoureteral reflux in children with voiding dysfunction. *J. Urol.* 2003; **169**: 1842–6.
24 Elder JS, Peters CA, Arant BS *et al.* Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J. Urol.* 1997; **157**: 1846–51.
25 Kirsch AJ, Arlen AM, Leong T *et al.* Vesicoureteral reflux index (VURx): a novel tool to predict primary reflux improvement and resolution in children less than 2 years of age. *J. Pediatr. Urol.* 2014; **10**: 1249–54.
26 Estrada CR Jr, Passerotti CC, Graham DA *et al.* Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J. Urol.* 2009; **182**: 1535–41.
27 Sillén U, Brandström P, Jodal U *et al.* The Swedish reflux trial in children: v. Bladder dysfunction. *J. Urol.* 2010; **184**: 298–304.