

The results of three times repeated filling cystometry and pressure flow studies in children with non-neurogenic lower urinary tract dysfunction

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Abstract

Aim: We previously reported that some urodynamic parameters change with repetitive filling in children with neurogenic lower urinary tract dysfunction (LUTD). In this study, we aimed to search if three-times repeated filling cystometries (FC) and pressure-flow studies (PFS) would change the urodynamics parameters in children with non-neurogenic LUTD.

Materials and Methods: All children with three repeated FC and PFS between June 2017 and December 2018 were included in the study. Urodynamic reports and charts were evaluated retrospectively. The first sensation of bladder filling (FSBF), maximum cystometric capacity (MCC), detrusor pressure at the FSBF ($P_{\text{det.first.sens}}$), maximum detrusor pressure during filling ($P_{\text{det.fill.max}}$), presence of detrusor over activity, compliance, maximum urine flow (Q_{max}), detrusor pressure at the maximum urine flow ($P_{\text{det}Q_{\text{max}}}$), residual urine and presence of detrusor sphincter dyssynergy (DSD) were compared among three-times repeated urodynamic studies.

Results: Forty children were included in the study. 27 (67.5%) were girls and 13 (32.5%) were boys. Median age was 9 (3.4–17) years. Indications were LUTD with low grade vesicoureteral reflux in 19 (47.5%), LUTD refractory to conservative management in 13 (32.5%), urinary tract infection with LUTD in 6 (15%) and secondary enuresis in 2 (5%). $P_{\text{det.first.sens}}$, presence of DO, MCC, Q_{max} , $P_{\text{det}Q_{\text{max}}}$, residual urine, flow pattern, and presence of DSD were comparable in all three repeated tests. The third FC may show decreased filling detrusor pressures and increased compliance with no change on capacity.

Conclusion: In children with non-neurogenic LUTD, three-times repeated FC and PFS present comparable results except FSBF, $P_{\text{det.fill.max}}$, and compliance at the third test.

KEYWORDS

children, detrusor, lower urinary tract dysfunction, overactivity, repeating, urodynamics

1 | INTRODUCTION

In children, lower urinary tract symptoms unassociated with anatomical or neurological disorders are considered functional bladder disorders.¹ These symptoms may be in the period of urine storage or voiding. Lower urinary tract dysfunction (LUTD) consists of different pathologies such as from overactive bladder to dysfunctional voiding. In the initial evaluation of LUTD, urine analyses, ultrasonography (US), and noninvasive urodynamic studies such voiding diary, questionnaires, uroflowmetry, and measurement of post voiding residual (PVR) urine volume should be performed.² Invasive urodynamic studies are recommended when neurological deficits are suspected or there is an unanswered question in the initial evaluation.² Detrusor over activity (DOA), maximum cystometric capacity (MCC), compliance, maximum detrusor pressure at filling ($P_{\text{det.fill.max}}$) in filling cystometry, and maximum urine flow (Qmax), detrusor pressure at the maximum urine flow (PdetQmax), residual urine and presence of detrusor sphincter dyssynergy (DSD) in pressure-flow studies (PFS) are some of the important parameters for the management of LUTD. Especially in children, anxiety and communication problems are serious problems during urodynamic examinations and can cause skeptical results. Therefore, International Children's Continence Society (ICCS)² and the European Society for Pediatric Urology (ESPU)³ recommend at least two complete cycles (filling and voiding) in the same session. We recently reported a significant decrease at $P_{\text{det.fill.max}}$ and detrusor leak point pressure (DLPP) but no change in MCC in repeated in filling cystometries (FC) in children with neurogenic LUTD due to myelodysplasia.⁴ Interestingly, although there is some data on consistency of urodynamic parameters on repetitive filling cystometry in children with non-neurogenic LUTD, PFS has not been compared efficiently. Furthermore, the urodynamics procedures of those studies are not compliant with recommendations by ICCS and International Continence Society (ICS) in terms of filling rate, and catheter size.

We hypothesized that FC and PFS parameters may change by consecutive cycles in children with non-neurogenic LUTD and tested it by comparing reports and charts of three consecutive same session urodynamics applicable with current urodynamics standardization guidelines.

2 | MATERIALS AND METHODS

We retrospectively searched for urodynamics reports of children with LUTD between June 2017 and December 2018. We included only the first three consecutive same

session urodynamics studies for children and excluded all children with neurogenic LUTD (myelodysplasia, cerebral palsy, spinal cord injury, etc.), high grade (Grade IV–V) vesicoureteral reflux (VUR) and prior any surgical intervention on lower urinary tract. Patients' characteristics and disease-related factors and urodynamics parameters were evaluated and recorded. Ethical approval was obtained from the local ethics committee before the study (2021/01-07).

Children with LUTD were evaluated by physical examination, urine analysis, urine culture, urinary system US, voiding diary, uroflowmetry, ultrasound measurement of PVR. We performed urodynamics if these conditions were present: High PVR or LUTD resistant to standard urotherapy (conservative management with biofeedback) and medical therapy (oral anticholinergics) or LUTD accompanied by vesicoureteral reflux (VUR) or recurrent urinary tract infections (UTI) or secondary enuresis. We routinely perform urodynamic studies in children with both VUR and refractory LUTD before decision-making of the surgical intervention in our clinic. Some children with urgency or urge incontinence were already on anticholinergic treatment and some of them with VUR or UTI were on antibiotic prophylaxis. A urodynamic study was performed when the urine culture was sterile and after anticholinergics were stopped at least for 2 weeks. Children with UTI were treated with antibiotics appropriate for a urine culture before the procedure.

All urodynamic studies and reporting were performed as recommended by ICCS. Our urodynamic procedure was described before.⁴ Urodynamic studies were performed with specific hardware called Locum Wireless Urodynamic System. Every study was performed in supine position with a transurethral 6 Fr urodynamic catheter without any sedation. The expected bladder capacity (EBC) according to age was calculated with a formula: $(\text{age} \times 30) + 30$ and the filling rate was taken as 10% of the expected bladder capacity according to age per minute.² Filling was performed with 0.9% saline at body temperature. The procedure was terminated when continuous urinary incontinence happened and/or persistent detrusor pressure ≥ 40 cmH₂O was observed. Bladder pressure changes occurring during crying, coughing, and moving were accepted as artifacts. Credé maneuver was not used during filling cystometry. After FC, PFS was performed in all children. The PFS starting point was accepted when the child and urodynamicist allowed voiding or when involuntary voiding began.⁵ In very young children it is not always possible to follow voiding instructions and DOA can be confused with voiding detrusor pressure. Therefore, DOA at the near-maximum capacity was neglected and

TABLE 1 Comparison of the variables between filling cystometry

	First filling cystometry (n = 40)		Second filling cystometry (n = 40)		Thrd filling cystometry (n = 40)		p Value
	Median	IQR	Median	IQR	Median	IQR	
FSBF ⁶	98	60.8	120.5	114	131	125.8	<0.001^a 0.076 ¹⁻² 0.030²⁻³ <0.001¹⁻³
P _{det.first.sens} (cmH ₂ O)	11.50	17.25	10.00	13.00	8.00	13.75	0.533 ^a
MCC ⁶	198.5	190	225	182.3	240.5	120.3	0.407 ^a
P _{det.fill.max} (cmH ₂ O)	40.0	60	23.5	52.3	22.5	44.0	0.027^a 0.221 ¹⁻² 1.000 ²⁻³ 0.030¹⁻³
Compliance (ml/cmH ₂ O)	5.2	10.8	7.1	15.0	10.0	20.5	0.007^a 0.172 ¹⁻² 0.656 ²⁻³ 0.005¹⁻³
DOA	Absent (% (n))	22.5 (9)	32.5 (13)		35.0 (14)		0.211 ^b
	Present (% (n))	77.5 (31)	67.5 (27)		65.0 (26)		
MCC/EBC (%)		76.9	72.4	77.1	57.9	82.8	46 0.407 ^a

Note: 1–2 Paired wise comparison analysis: First versus second cystometry; 2–3 Paired wise comparison analysis: First versus third cystometry; 1–3 Paired wise comparison analysis: First versus third cystometry).

Abbreviations: DOA, detrusor overactivity; EBC, expected bladder capacity; FSBF, first sensation of bladder filling; IQR, interquartile range; MCC, maximum cystometric capacity; P_{det.first.sens}, detrusor pressure at the FSBF; P_{det.fill.max}, maximum detrusor pressure during filling.

^aRepeated samples Friedman two-way analysis of variance by ranks.

^bRelated-sample cochrane Q Test.

interpreted as normal.² Bladder volume at first sensation during bladder filling (FSBF), detrusor pressure at FSBF (P_{det.first.sens}), MCC, P_{det.fill.max}, DOA, compliance, P_{detQ-max}, DSD and MCC/EBC were calculated and evaluated according to the definitions of ICCS standardization report.² Bladder compliance is calculated on the basis of the difference between the initial resting pressure and the detrusor pressure at cystometric capacity. Detrusor overactivities during filling were omitted in the calculation of the compliance. These parameters in all three-repeating FC and PFS were compared with each other. All repeated studies were interpreted by RE.

2.1 | Statistical analysis

Statistical analyses were performed using the statistical analysis program package IBM SPSS Statistics (Version 25.0; IBM Corp.) and R statistical package (version 3.6.2; the R foundation for Statistical Computing). Variables of

urodynamic studies did not show a normal distribution in Shapiro–Wilk test and the statistical analysis were performed with nonparametric tests. For continuous variables, related samples Friedman's two-way analysis of variance by rank were used. Significance values of pairwise comparisons were adjusted by the Bonferroni correction for multiple tests. Continues variables were given as median and interquartile range (IQR). For binary responses found in urodynamic studies were analyzed with related samples Cochran's Q-test. Variables of FC and PFS were shown with boxplot graphs. Tests were considered significant for $p < 0.05$.

3 | RESULTS

We found 52 children with non-neurogenic LUTD who underwent urodynamic studies for the first time in the study period. 40 children, 27 (67.5%) were girls and 13 (32.5%) boys, met the inclusion criteria. The other 12

TABLE 2 Comparison of the variables between pressure-flow studies

	First pressure-flow (<i>n</i> = 40)		Second pressure-flow (<i>n</i> = 40)		Third pressure-flow (<i>n</i> = 40)		<i>p</i> Value
	Median	IQR	Median	IQR	Median	IQR	
PdetQmax (cmH ₂ O)	34	30.80	31	28	35.5	23.00	0.760 ^a
Qmax (ml/sn)	11.5	9	13.0	8.5	15.0	32.0	0.589 ^a
Residual urine ⁶	6.5	52.3	5.0	44.5	5.0	35.8	0.130 ^a
DSD	Absent (% , (<i>n</i>))	45 (18)	40 (16)		52.5 (21)		0.422 ^b
	Present (% , (<i>n</i>))	55 (22)	60 (24)		47.5 (19)		
Voiding pattern	Normal (% , (<i>n</i>))	57.5 (23)	65 (26)		65 (26)		0.589 ^b
	Abnormal (% , (<i>n</i>))	42.5 (17)	35 (14)		35 (14)		

Note: 1–2 Paired wise comparison analysis: First versus second cystometry; 2–3 Paired wise comparison analysis: First versus third cystometry; 1–3 Paired wise comparison analysis: First versus third cystometry.

Abbreviations: DSD, detrusor sphincter dyssynergia; IQR, interquartile range; PdetQmax, maximum detrusor pressure at maximum urine flow; Qmax, maximum urine flow.

^aRepeated samples Friedman two-way analysis of variance by ranks.

^bRelated-sample cochrane Q test.

children did not have three repeated FC and PFS at the same session due to inability to perform PFS (*n* = 6), spontaneous removal of the urethral or rectal catheter (*n* = 3), anxiety or adaptation problems (*n* = 3). The median age was 9 (3.4–17) years. Indications were LUTD with low grade (I–III) VUR in 19 (47.5%), LUTD with or without high PVR refractory to standard urotherapy and medical management in 13 (32.5%), UTI with LUTD in 6 (15%), and secondary enuresis in 2 (5%). LUTD included dysfunctional voiding and overactive bladder.

In three consecutive same session FCs, MCC, $P_{\text{det.first-sens}}$, presence of DOA, MCC/EBC ratio did not show any statistically significant difference (Table 1, Figure S1). However, as shown in Table 1 and Figure 1, FSBF of the third filling cystometry was significantly higher than the first and the second filling ($p < 0.001$, $p = 0.030$). The $P_{\text{det.fill.max}}$ value in the first filling cystometry was significantly higher than the third filling ($p = 0.030$). Compliance of the third filling was higher than the first filling ($p < 0.005$) albeit, we didn't observe any difference between the first and second filling.

DOA in the FC was present in 77.50% (31/40) in the first, in 67.50% in the second (27/40), and 65% (26/40) in the third (Cochran's Q test, $p = 0.211$). DOA was present in all three consecutive fillings in 47.5% ($n = 19/40$) and disappeared in 38.70% ($n = 12/31$), and appeared in 66.66% ($n = 6/9$) in cycling cystometries (Table 3).

As seen in Table 2 and Figure 2, in PFSs, we did not detect any difference in PdetQmax, Qmax, residual urine ($p = 0.760$, $p = 0.589$, $p = 0.130$, respectively). DSD and abnormal voiding pattern in the PFSs was present in 55% (22/40), 42.5% (17/40) in the first, in 60% (24/40), 35%

TABLE 3 Detrusor overactivity status of patients for each filling cystometry (Cochran's Q test, $p = 0.211$)

	First filling cystometry	Second filling cystometry	Third filling cystometry
Study group (<i>n</i> :40)	No DOA (<i>n</i> = 9)	No DOA (<i>n</i> = 5)	No DOA (<i>n</i> = 4)
			DOA (<i>n</i> = 1)
		DOA (<i>n</i> = 4)	No DOA (<i>n</i> = 2)
			DOA (<i>n</i> = 2)
	DOA (<i>n</i> = 31)	No DOA (<i>n</i> = 8)	No DOA (<i>n</i> = 4)
			DOA (<i>n</i> = 4)
		DOA (<i>n</i> = 23)	No DOA (<i>n</i> = 5)
			DOA (<i>n</i> = 18)

Abbreviation: DOA, detrusor overactivity.

(14/40) in the second, and 47.5% (19/40), 35% (14/40) in the third (Cochran's Q test, $p = 0.422$, and $p = 0.589$, respectively) (Table 2, Figure S2). DSD was present in all three consecutive PFSs in 25% ($n = 10/40$), disappeared in 62.96% ($n = 17/27$), appeared in 55.55% ($n = 10/18$) in repeated PFSs (Table 4), and abnormal voiding pattern present 17.5% ($n = 7/40$), disappeared 58.82% ($n = 10/17$), and appeared 30.43% ($n = 7/23$).

4 | DISCUSSION

Invasive urodynamic studies are the most sophisticated tests for evaluating lower urinary tract functions in children. In recent years, urodynamic studies have been

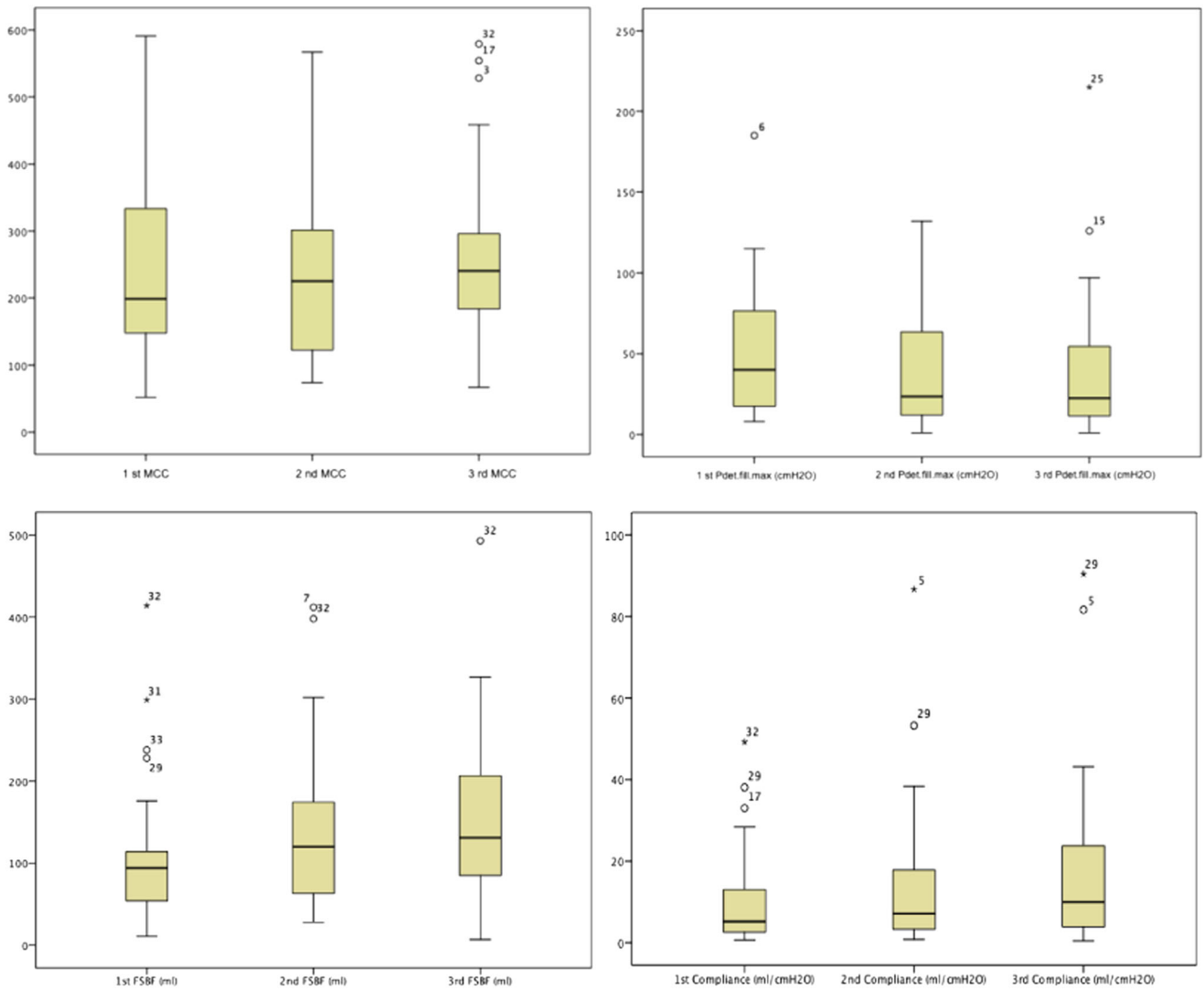


FIGURE 1 Maximum cytometric capacity, maximum detrusor pressure during filling, first sensation of bladder filling (FSBF), compliance for each filling cystometry cycle.

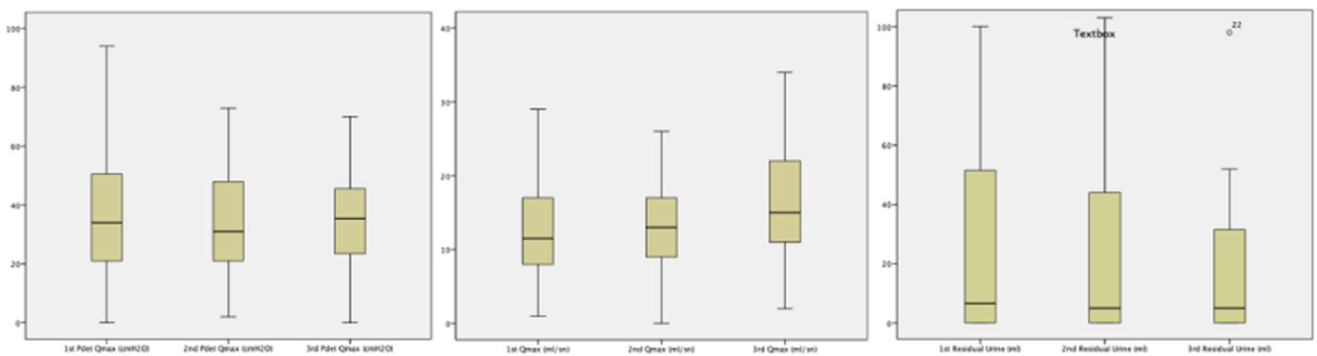


FIGURE 2 Detrusor pressure at the maximum urine flow (PdetQmax), maximum urine flow (Qmax), residual urine for each pressure-flow studies.

standardized according to guidelines recommended by ICS, ICCS, and ESPU for good clinical practice. Although at least two filling cystometries are recommended in the same session in children, the consistency between the

parameters of repetitive urodynamic studies is not clear. We recently showed that consecutive urodynamics present similar results except a significant decrease in $P_{det.fill.max}$ and DLPP in children with neurogenic LUTD.

	First pressure-flow	Second pressure-flow	Third pressure-flow
Study group (n:40)	No DSD (n = 18)	No DSD (n = 11)	No DSD (n = 8)
		DSD (n = 7)	No DSD (n = 3)
		DSD (n = 7)	DSD (n = 4)
	DSD (n = 22)	No DSD (n = 5)	No DSD (n = 3)
		DSD (n = 17)	DSD (n = 2)
			No DSD (n = 7)
		DSD (n = 10)	

Abbreviation: DSD, detrusor sphincter dyssynergia.

TABLE 4 Detrusor sphincter dyssynergia status of patients for each pressure flow study (Cochran's Q test, $p = 0.422$)

Therefore, this time, in this study, we aimed to test our first hypothesis in non-neurogenic LUTD children. Interestingly, the present study also showed very similar results with our former study in terms of decreasing $P_{\text{det.fill.max}}$ particularly in the third cycle in children with non-neurogenic LUTD.

We believe that urodynamics presents solid data in terms reproducibility and validity in children if performed under standardized guidelines. Our former data shows that detrusor pressures in the filling phase and during urethral leaking tend to decrease with repeating cycles in the same session. The reason for such tendency has been speculated as stress relaxation due to intrinsic viscoelastic properties of the detrusor muscle.^{7,8} Present study confirms our prior observations on detrusor pressure decrease with repeated cycles with a specific notice on the third cycle. However, detrusor pressures during voiding are very stable in all three cycles in children with non-neurogenic LUTD.

Although urodynamics is the most important test in evaluation and management of children with neurogenic LUTD, its role is much limited in non-neurogenic cases. The indications for urodynamic study in non-neurogenic LUTD have been suggested as voiding frequency <3 per day, straining or manual expression during voiding, a weak urinary stream, urge incontinence resistance to treatment, stress incontinence, or new or worsening dilating vesicoureteral reflux, recurrent UTI.² Our urodynamic investigation indications were high PVR or LUTD resistant to standard urotherapy (conservative management with biofeedback) and medical therapy (oral anticholinergics) or LUTD accompanied by vesicoureteral reflux (VUR) or recurrent UTI or secondary enuresis. The findings in urodynamics can help us in differentiating severe detrusor overactivity, detrusor pressure issues, or severe compliance problems leading to further spinal abnormality search and primary bladder neck dysfunction.

Our previous study revealed a change only in two variables with repeated filling studies, a decrease in $P_{\text{det.fill.max}}$ and DLPP. All other measurements such as MCC, MCC to EBC rate, and PVR were found to be similar in consecutive studies. Surprisingly, DOA rates were found to be similar in all three fillings but acted differently: in four children DOA disappeared and in five children DOA was established in repeated tests. All procedures of the urodynamics investigations of the present study were carried out similarly to our previous study. Likewise, a cohort of the present study had similar DOA rates in filling studies but, the DOA rate of the non-neurogenic group was smaller compared to the previous study; 90% versus 77.5% in the first, 93.75% versus 67.5% in the second, and 91.25% versus 65% in the third study. In addition, DOA change pattern was more prominent in present study; in 30% ($n = 12$) DOA disappeared and in 15% ($n = 6$) DOA was established with repeated tests. However, in literature, DO inconsistency has been reported between repeated studies. In 1982, Griffiths and Scholtmeijer reported that detrusor instability decreased in consecutive urodynamics in children.⁹ Similarly, Chin-Peuckart et al. conducted two filling cystometry on 68 children and reported that uninhibited detrusor contractions decreased in the second fillings.⁶ Sozubir et al. retrospectively analyzed 70 children with detrusor instability who underwent repeated FC in the same session.¹⁰ They reported that the mean detrusor contraction was 6.6 in the first filling and 4.1 in the second, and 4.4 in the third. It was emphasized that DO can be provoked by anxiety or catheter irritation in children. In addition, it is also known that it is not always possible to demonstrate during urodynamic studies in patients with non-neurogenic LUTS. Digesu et al. evaluated urodynamics reports of 4500 women with symptoms consistent with an overactive bladder (urinary frequency, urgency, and/or urge incontinence) retrospectively, and found that only 18.7% of patients ($n = 843$) had urodynamically proven DO.⁴

Another important parameter in invasive urodynamic studies is MCC, and it appears to be quite consistent in consecutive fillings. Chin-Peuckert et al reported the MCC as 179 ± 109 ml at the first filling and 186 ± 123 ml at the second filling and did not find a statistically significant difference ($p = 0.33$).⁶ However, the patient group of this study was not homogeneous and consisted of 43 (65%) children with spinal dysraphism, 4 (6%) cerebral palsy, 5 (8%) posterior urethral valve, and 14 (21%) recurrent urinary tract infection, daytime incontinence, and frequency/urgency symptoms. Sozubir et al. calculated the mean bladder capacity/expected bladder capacity ratio for three consecutive FC and reported that they were similar (0.861, 0.889, and 0.868, respectively).¹⁰ In our previous study, we also observed that all MCC and MCC/EBC (%) were consistent with each other in children with myelodysplasia. In the present study, median MCC (IQR) and MCC/EBC (%) (IQR) were found to be 198.6 ml (190), 76.9% (72.4) in the first filling, 225 ml (182.3), 77.1% (57.9) in second filling and 240.5 ml (120.39), 82.8% (46) in third filling, and there was no significant difference ($p = 0.407$, $p = 0.407$, respectively). Bladder compliance values were higher in the third cystometry compared with the first ($p = 0.005$). We found the compliance values for consecutive fillings as 5.2 ml/cmH₂O (10.8), 7.1 ml/cmH₂O (15), 10 ml/cmH₂O (20.5), respectively. We think that the improvement of bladder compliance is associated with decreased detrusor pressures on repetitive filling.

In the literature, there is not sufficient data about the consistency of the PFS in children and it was evaluated for the first time in this study. Tammela TLJ et al. reported the results of three consecutive PFSs performed by suprapubic urodynamic catheter in patients with lower urinary tract symptoms due to benign prostatic hyperplasia (BPH).¹¹ In this study of 187 patients (mean age 67 years), maximum flow rate (7.4, 7.5, and 7.3 ml/sn), residual volume (80, 90, and 115 ml), and voided volume (292, 280, and 271 ml) were similar between all three studies, whereas a significant decrease was found in PdetQmax (71.0, 66.5, and 63.0 cmH₂O). Another study of 91 patients (mean age 61.6 years with BPH) showed a similar decrease in PdetQmax (74.4 cmH₂O vs. 71.4 cmH₂O) in the second PFS.¹² In the same study, bladder capacity, residual volume, and maximum flow rate were similar among the two studies. In a study of 152 women with urinary incontinence, the reproducibility of the same session repeated PFSs were reported to be overall good to excellent.¹³ In this study, all parameters of PFS were consistent among three consecutive fillings, and these findings were parallel to adult urodynamic studies except PdetQmax. Also, it has been reported that voiding curves may change in repetitive uroflowmetry in relation to voided volume.¹⁴ However, voiding patterns

were observed to be similar among the three PFSs in our study. We consider that voiding patterns don't affect to results of PFS and a single PFS seems to be sufficient.

We perform the urodynamic studies in accordance with the guidelines of ICCS.² Therefore, we preferred body temperature for retrograde saline filling during cystometry in children. However, we know that there is a lack of data in the literature on the impact of fluid temperature on urodynamic findings and clinical outcomes. In a study, it was reported that the cystometric bladder capacity, detrusor pressures were lower and, the maximum flow rate was higher in children filled at body temperature than in children filled at room temperature.¹⁵ In the same study, detrusor leak point pressure, pressure at maximum flow, maximum voiding pressure, and residual urine were found similar between body and room temperature. Interestingly, DOA was more frequent during infusions at room temperature. Although the authors were unsure of the clinical effect, they recommended the use of warm saline for filling cystometry, particularly in children younger than 2 years of age. It can be speculated that the studies designed with saline at room temperature may provoke DOA.

The present study has some limitations. There was no patient with severe non-neurogenic bladder dysfunction such as posterior urethral valve and Ochoa syndrome in this study. No patient was on clean intermittent catheterization. We also did not compare the PFS for changing flow patterns. However, we observed that the detrusor pressure change was related to the number of fillings. It can be argued that if the results of two repeated tests are inconsistent in terms of lower urinary tract symptoms, voiding diary or uroflowmetry, a third one should not be performed in the same session. If necessary, a new FC can be performed in another session. We updated our clinical approach on urodynamic evaluations after these findings, and now we perform only two repeated fillings at the same session. As this study focused on urodynamic studies, findings on voiding diary were not evaluated. Provoked DOA by coughing, crying was not evaluated separately. We didn't evaluate anxiety and comfort level for each FC in this study. We didn't perform subgroup analysis because of the small number of cases. In this study, the conservative approach and medical treatment outcomes of the pre-urodynamic period were not reported.

5 | CONCLUSION

Consecutive urodynamic studies of children with non-neurogenic LUTD present consistent results in filling and voiding phases. However, the third FC may show decreased filling detrusor pressures and increased compliance with no change in capacity and PFS parameters.

AUTHOR CONTRIBUTIONS

Raziye Ergun: Concept—design, data collecting, data interpretation, manuscript drafting and writing, and literature screening. **Cagri Akin Sekerci:** Data interpretation, manuscript drafting, and writing, statistical analysis, and literature screening. **Yiloren Tanidir:** Data interpretation and statistical analysis. **Naime İpek Ozturk:** Data collecting. **Tufan Tarcan:** Supervision. **Selcuk Yucel:** Data interpretation and supervision.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT


The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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