Children with Non-Neurogenic Lower Urinary Tract Dysfunction Require Less Frequent and Number of Botulinum Toxin Injections Than Neurogenic Ones

Kamranbay Gasimov[1], Ruslan Jafarov[2], Vasileios Tatanis[1], Ali Cansu Bozacı[1], Erman Ceyhan[2], Turan Mammadaliyev[2], Hasan Serkan Doğan[1], Serdar Tekgül[1]

[1]Hacettepe University Faculty of Medicine, Department of Urology, Division of Pediatric Urology, Ankara, Turkiye
[2]Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkiye

---

What's known on the subject? and What does the study add?

Despite having different etiologies, neurogenic bladder and non-neurogenic lower urinary tract pathologies have similar clinical presentation and common symptoms. In our study, we aimed to point out the clinical outcome differences (duration of response and requirement for repeat injections) in different patient groups. In addition, the number of patients is considerably high for a single institute. There is only one study including a group larger than 89 patients (257 patients). The other studies were mostly conducted in patient groups of less than 60 cases.

Abstract

Objective: To evaluate pediatric patients with lower urinary tract dysfunction (LUTD) who received bladder or external sphincter botulinum toxin A (BTX) injection in terms of effectiveness and permanence.

Materials and Methods: We analyzed 80 patients treated with intradetrusor (n=48) n or intrasphincteric (n=32) BTx injection between May 2007 and December 2019. We divided the patients into 2 groups: Neurogenic bladder (NB) and LUTD. Clinical assessment of results was mainly done with Dysfunctional Voiding and Incontinence Symptoms Score (DVISS) and quality of life questionnaires and dryness status. Uroflowmetry with electromyography and video-urodynamic study was performed postoperatively.

Results: Mean age and follow-up time were 123.0±48.3 and 30.1±5.8 months. For bladder BTx (NB: 18 patients; LUTD: 30 patients), the response rate was 79.1% (n=38). NB patients' response duration was shorter (32 vs 87 weeks) and required subsequent multiple injections more (55% vs 23%) than the LUTD group. For sphincter BTx (NB: 13 patients; LUTD: 19 patients) clinical improvement was found in 75% (n=24) n of the patients. There was no significant difference between the NB and LUTD groups. DVISS and quality of life questionnaires showed substantial decrease in the LUTD groups after bladder (p<0.001) and sphincter (p<0.05) BTx injection. NB patients showed significant dryness status in both BTx-B (pre: 3.2%, post: 82.1%, p<0.05, chi-square test) and BTx-S (pre: 0%, post: 100%, p<0.05, chi-square test) patients postoperatively.

Conclusion: This study demonstrated that BTx injection is an effective and safe treatment in pediatric patients with NB and LUTD. With its benefits, this endoscopic treatment should be kept in mind before major constructive surgeries.

Keywords: Urodynamics, botulinum toxin A, luts

Introduction

Lower urinary tract dysfunction (LUTD) denotes any deviation from normal physiological storage and emptying functions of the bladder. Symptoms can be listed as daytime frequency, incontinence, urgency, nocturia, hesitancy, straining to void, weak caliber, intermittent urination, dysuria, post-voiding dribbling (1).

The etiology of LUTD can be divided into two basic categories: Neurogenic and non-neurogenic. Neurogenic LUTD is an abnormality of bladder and/or sphincter innervation and is due to congenital anomalies or acquired conditions (2).

Neurogenic bladder (NB) treatment aims at preservation of the upper urinary tract with low bladder pressure and normal compliance. CIC and antimuscarinic medications are initial tools to manage this condition (3).

Non-neurogenic LUTD can be identified within a spectrum of conditions starting from detrusor instability to serious cases affecting the upper urinary tracts without any known neurologic cause. Treatment aims at normalizing the voiding pattern and pelvic floor activity, incontinence and urinary tract infections. Physiotherapy, biofeedback, antimuscarinic and alfa-blocker medications, antibiotics can be used depending on the type and severity of symptoms at initial diagnosis (4).

Patients who do not benefit from initial treatment modalities, would need more invasive options ranging from endoscopic injection to open surgery like bladder augmentation. Botulinum toxin (BTx) injection with cytoscopic guidance into the detrusor or external urethral sphincter (EUS) is efficient in decreasing muscle overactivity with no serious side effects by interfering with SNAP proteins and blocking neurotransmitter release into the synaptic cleft (5). This is the most up-to-date alternative that can be used before irreversible surgical treatments.

Our hypothesis in this study is that BTx application to the detrusor and/or sphincter is an effective and safe treatment in non-neurogenic and neurogenic LUTD. For this purpose, we retrospectively evaluated pediatric patients who received BTx treatment.

Materials and Methods

This retrospective clinical study (Hacettepe University Local Ethic Committee, approval number: GO-18/449, date: 15.05.2018) included 89 patients who were treated with bladder or sphincter botulinum toxin A (BTX) injection between May 2007 and December 2019. Patients were given detailed information about the procedure and informed consent was obtained.

The indication for the procedure was the absence of clinical response to treatment for detrusor and/or sphincteric overactivity [standard urotherapy, medications, clean intermittent catheterization (CIC)] in non-neurogenic and neurogenic LUTD patients. None of the NB had a history of augmentation, cathaterizable stoma, or bladder neck surgery. In LUTD patients, the decision of response to medical treatment was given after at least 6 months of continuous use of antimuscarinics. Video-urodynamic study (VUDS) was applied to all patients. VUDS was performed in patients with sterile urine culture. During the procedure, a 7 Fr cystometry and rectal catheters were placed into the bladder and rectum. The bladder was filled with saline at room temperature at a rate of 5-10% mL/min of expected bladder capacity. Cystometric capacity, bladder and detrusor pressure, bladder compliance, bladder activity, were recorded. Bladder capacity and pressure at the initiation of reflux were recorded, if present. At the end, residual urine was calculated. Uroflowmetry (UF) with electromyography (EMG) was performed in all patients with dysfunctional voiding. Inclusion criteria for sphincter BTx were inefficient emptying with high-postvoiding residual volume, urinary incontinence and/or voiding symptoms with pathological UF pattern and EMG activity during urination in at least 2 consecutive tests.

BTX was injected into detrusor only, sphincter only and detrusor and sphincter simultaneously in 48, 32, and 9 children, respectively. BTX was injected with the guidance of a rigid cystoscope under general anesthesia in the presence of sterile urine. The total dose of BTX was 150-200 IU for the bladder with 20 injection sites sparing the trigone (6) (10 IU/kg, maximum total dose 200 IU), 50 IU for the sphincter diluted in 4 mL saline (12.5 IU/mL), were injected in 4 quadrants (3, 6, 9 12 o'clock positions) CITATION (7). Clinical outcomes were assessed with questionnaires including symptoms, postoperative UF and VUDS if parents approved. Demographic parameters (age, sex), the number of injections, clinical benefit, Dysfunctional Voiding and Incontinence Symptoms Score (DVISS), quality of life (QoL), dryness between CIC, time to initiate the effect and duration of efficacy, urodynamic parameters were recorded and compared before and after BTx injection. Efficacy parameters were continence or decrease in total number of incontinence episodes, prolonged dry time, normalized voiding pattern, decrease in DVISS score, cessation of recurrent urinary tract infections. Indications for repeat injections were recurrence of symptoms.

Statistical Analysis

In the statistical comparison of the data, chi-square test, Mann-Whitney U test, t-test were used with the Statistical Package for Social Sciences (SPSS 17.0). A p-value less than 0.05 in the 95% confidence interval was considered statistically significant.

Results

Since the number of patients who underwent simultaneous bladder and sphincter injections was small, the statistical analysis was performed in those with detrusor only and sphincter only cases. Mean age of first application and follow-up was 123.0±48.3 and 30.1±5.8 months, respectively. Female/male ratio was 44/36. 58% of the children had LUTD, whereas 42% of them had NB. The causes of NB were spina bifida and myelomeningocele.

Clinical improvement was observed in 83.3% (40) of who received BTx injection to the bladder (BTx-B) after a median number of 1 (1-3) injection. NB patients had a shorter duration

of response (32 vs 87 weeks) and required more injections than LUTD patients (55% vs 23%) (Table 1).

Clinical improvement after BTx injection to sphincter (BTx-S) was observed in 75% (24) children with a median number of 1 (1-2) injection with a mean duration of action of 27.8±25.7 weeks. There was no statistically significant difference between NB (n=13) and LUTD (n=19) in terms of response parameters (Table 2).

The DVISS and QoL scores of the LUTD group decreased significantly in the postoperative period who underwent BTx-B and BTx-S (Table 2). NB patients were evaluated with dryness status between CIC before and after BTx injection. The results showed a statistically significant difference with 82.1% (pre: 3.2%, post: 82.1%, p<0.05, chi-square test) and 100% (pre: 0%, post: 100%, p<0.05, chi-square test) dryness after the BTx-B and BTx-S group, respectively.

Although, all patients underwent preoperative VUDS, only the parents of 29 patients allowed us to perform postoperative VUDS. The comparison of pre- and post-operative urodynamic studies in 29 children revealed increased bladder capacity (V_{max}), decreased $Pdet_{max}$ and $Pves_{max}$. However, decreases in $Pdet_{max}$ and $Pves_{max}$ were significant in LUTD patients where the increase in V_{max} was significant in NB patients (Tables 3 and 4). VUDS in these patients revealed improvement in detrusor overactivity (presence of detrusor overactivity, preoperative: 71.1% vs postoperative: 55.6%, p=0.037, McNemar test) and compliance (presence of hypocompliance, preoperative: 71.4% vs postoperative: 52%, p=0.039, McNemar test). Detrusor reflex volumes (DRV) increased after the procedure in both LUTD [from 51.00 (4.00-275.00 to 148.00 (21.00-647.00) mL, Wilcoxon signed-rank test, p=0.001] and NB (from 61.5±62.4 mL to 98.4±86.2 mL, paired Sample t-test, p=0.029) patients. There was no statistical significant difference in preoperative DRV patients with and without clinical response [mean preoperative DRV with and without clinical response: 72.00 (2.00-524.00), 97.75 (3.00-492.00), respectively, p=0.850, Mann-Whitney U test].

One BTx-B patient had urinary retention in the postoperative period requiring catheterization for 24 h. There was no

Table 1. Demographic parameters

Parameter	BTx-B		Sphincter Btx	
	Neurogenic bladder (n=18)	Lower urinary tract dysfunction (n=30)	Neurogenic bladder (n=13)	Lower urinary tract dysfunction (n=19)
Boy/girl	10/8	11/19	7/6	3/16
Age (median, min-max)	156 (72-324)	114 (70-205)	129 (94-180)	117 (60-208)
Number of injections (median, min-max)	1 (1-3)	1 (1-3)	1 (1-2)	1 (1-2)
Clinical benefit (yes/no)	15/3	23/7	8/5	16/3
Time to effect, week (median, min-max)	2 (0-8)	2 (0-8)	2 (0-4)	2 (0-4)
Duration of efficacy, week (median, min-max)	32 (11-120)	87 (12-465)	24 (12-64)	29 (5-96)
Single injection/multiple injections	8/10	23/7	13/0	17/2
Min-max: Minimum-Maximum, BTx: Botulinum toxin				

Table 2. Comparison of DVISS and QoL scores of LUTD patients

Parameter	BTX-B			BTX-S		
	pre	post	p	pre	post	p
DVISS (mean ± SD)	20.80±6.39	10.20±7.62	<0.001[a]	16.63±6.12	8.16±7.37	<0.001[a]
QoL (mean ± SD)	2.60±0.77	1.33±1.12	<0.001[a]	2.79±0.78	1.16±1.21	<0.001[a]
DVISS + QoL (mean ± SD)	23.51±6.55	12.81±7.71	<0.001[a]	19.25±6.5	11.06±8.04	0.00[a]
[a]: Paired sample t-test, SD: Standard deviation, BTX: Botulinum toxin A, DVISS: Dysfunctional Voiding and Incontinence Symptoms Score, QoL: Quality of life, LUTD: Lower urinary tract dysfunction						

Table 3. Comparison of preoperative and postoperative urodynamic parameters of bladder BTx injection (LUTD group) patients

Non-neurogenic LUTD (n=23)	V_{max} (mean)	$Pdet_{max}$ (mean)	$Pves_{max}$ (mean)
Preoperative	247 mL	70 cmH$_2$O	76 cmH$_2$O
Postoperative	266 mL	47 cmH$_2$O	56 cmH$_2$O
p	0.281a	0.030[a]	0.024[a]
[a]: Paired sample t-test, LUTD: Lower urinary tract dysfunction, BTx: Botulinum toxin			

urinary tract infection after the procedure and 1 patient had postoperative pain.

Nine patients who underwent simultaneous bladder and sphincter injections had a mean age of 135.89±34.09 and male-to-female distribution of 5/4. Four of 9 had neurogenic origin. Seven (77.7%) patients benefited from the treatment. None of them experienced complication.

Discussion

The BTx injection is also a very useful treatment option in LUTD and NB patients who do not respond to initial non-invasive treatment modalities with incontinence or repeated urinary infections (8). These toxins are composed of two chains and three functional domains: The light chain (LC, ~50 kDa), which is a zinc-dependent metalloprotease that cleaves the target proteins in neurons, and the heavy chain (HC), which can be further divided into the N-terminal membrane translocation domain (HN, ~50 kDa) and the C-terminal receptor-binding domain (HC, ~50 kDa). There are 7 serotypes of botulinum neurotoxins but only botulinum-A serotype is U.S. Food and Drug Administration-approved for medical uses in humans (9). There are two subtypes of botulinum-A serotype neurotoxin, onabotulinum-A (Botox@) and abobotulinum-A neurotoxin (Dysport@). The onabotulinum-A is mainly used in urology, whereas abobotulinum-A plays a critical role mainly in dermatological interventions. However, many studies on the effect of botulinum injection in the lower urinary tract is present using the abobotunlinum-A toxin (9). EAU guidelines recommend the onabotulinum-A toxin injection as a treatment option for patients with idiopathic or NB overactivity refractory to the first-line treatment with anticholinergic agents (10). In the pediatric population, the role of onabotulinum-A toxin injection is the preservation of renal function preventing the urinary infections in patients with bladder overactivity or NB. It is also recommended as a treatment option in patients with incontinence refractory to the anticholinergic agents (11). As for the dose, 5 U/kg and 10 U/kg doses have been tested in the literature (12,13). It comprises a very promising intervention as it can achieve continence, increase in maximum cystometric capacity and improvement of compliance and maximum detrusor pressure (12). Studies with higher doses (12 IU/kg, maximum 300 IU) reported similar clinical results (13). We used a dosage of 10 IU/kg (not exceeding a total dose of 200 IU) and achieved symptomatic improvement in ¾ of our patients. Recently, the experimental use of electromotive drug administration (EMDA) has been investigated with the aim of increasing drug delivery. It was hypothesized that EMDA provide better BTx delivery into the deeper detrusor muscle layers. Kajbafzadeh et al. (14) showed that the EMDA system, in moderate to severe incontinent NB patients, provided urinary continence in 70% and improvement in constipation in 77%.

In a recent review, the clinical response to intradetrusor BTx injection was reported to a range of 65-87% (6). In our study, the indication for the application of onabotulinum-A injection in the NB group was the repeated urinary infection or the urinary incontinence refractory to first-line treatment with anticholinergic agents. We evaluated the clinical improvement after the bladder injection using the dryness status. Clinical improvement was observed in 82.1% patients, which were statistically significant. Being more significant than the mentioned objective and subjective findings, we detected that many patients or the caregivers who benefited from the procedure, indicating that the timing of re-injection as the well-being starts to diminish in time. It was noticed that the effect of BTx injection lasted for 2-24 weeks in literature (6). We found that the mean duration of the effect persisted for 32 weeks for the bladder and 24 weeks for the sphincter injections. The systematic review of Hascoet et al. (12) showed that BTx injection provided improvements in urodynamic parameters as decreasing the $Pdet_{max}$ (32-54%) and increasing the V_{max} (27-162%) and compliance (28-180%). Another multicenter study in 53 NB patients reported 66% clinical improvement rate and 34% urodynamic success rate was that in fact showed discrepancy between clinical condition and laboratory tests (15). In our VUDs, only the V_{max} statistically significantly increased (pre-operatively 149 mL vs post-operatively 228 mL) (p<0.05) and the improvement in other parameters was not significant. However, the number of patients with postoperative VUD was small that decreases the reliability of the statistical analysis result. In terms of repeated injections, literature showed us great variance of rates from 9% to 47% (13). In our study, many NB patients (10/18; 55.5%) required more than 1 injection.

Regarding the group of LUTD, in the literature, clinical improvement after BTx injection for LUTD patients was 38-60%, whereas the mean efficacy duration was 32 weeks (12,16). In

Table 4. Comparison of preoperative and postoperative urodynamic parameters of bladder BTx injection (NB group) patients			
Neurogenic LUTD (n=6)	V_{max} (mean)	$Pdet_{max}$ (mean)	$Pves_{max}$ (mean)
Preoperative	149 mL	44 cmH$_2$O	43 cmH$_2$O
Postoperative	228 mL	27 cmH$_2$O	37 cmH$_2$O
p	**0.028**[a]	0.295[a]	0.557[a]
[a]: Paired sample t-test, LUTD: Lower urinary tract dysfunction, BTx: Botulinum toxin, NB: Neurogenic bladder			

a recent study, 257 patients underwent onabotulinum-A toxin injection in a fixed dosage of 100 U. Study reported 50% and 45.7% full clinical response rates in patients with enuresis and daytime incontinence, respectively. The cystometric capacity increased by 23.1%, 31.6% and 16.8% after the first, second and third injections. One patient developed post-operatively urinary retention, which was resolved with temporary CIC (16). In our study, onabotulinum-A toxin injection was applied to LUTD patients with incontinence or urinary infection refractory to first-line treatment with anticholinergic agents. Clinical benefit was investigated in 79.6% (29/39) and the mean duration of effect was 87 weeks for the bladder injection and 29 weeks for the sphincter injections. In this LUTD group, multiple injections were required in 7 of 30 BTx-B and 2 of 19 BTx-S patients. In VUDS, the post-operative improvement was statistically significant in $Pdet_{max}$, $Pves_{max}$ and compliance. We evaluated the clinical improvement by using DVISS and QoL questionnaires. All DVISS, QoL, DVISS+QoL scores were statistically significantly improved after BTx injection. The only study comparing DVISS scores in the literature was conducted in patients who received bladder injections and demonstrated well-being status up to 12 months postoperatively (17). We used this specific scoring system for the evaluation of both bladder and sphincter injections. In our study, the pre- and post-operative DVISS values were 20.67 and 10.67 (p<0.05) for the bladder, and 16.75 and 8.93 (p<0.05) for the sphincter BTx injection patients, respectively.

After the effect of onabotulinum-A in the vesical non-sympathetic synapses, the neuron starts forming new synapses to replace the blocked ones. This process is called sprouting, however the original synapses regenerate and the neo-synapses degenerate. That is the cause of the temporary effect of the intradetrusor or intrasphincteric onabotulinum-A injection (18). The effect of onabotulinum-A toxin on the target-tissue starts in only a few days and reaches its peak after 2-6 weeks. After the peak point, the effect of onabotulinum-A toxin decreases gradually to a minimum level after 6-12 months (19). Antibodies directed against onabotulinum-A toxin interfere with the biological aspects of the toxin and may lead to an antibody-induced failure. The individual dose, the immunologic quality of the onabotulinum-A preparation and the interval between injections are determined as risk factors. The cumulative dose, the treatment time and the patients' age are not presented as related to antibody induced failure factors. Therefore, it is recommended that repeat injections should be performed at least 3 months after the previous one (20). In our investigation, in both the NB and LUTD groups the time to initiate effect was 0-2 weeks and the duration of the effect was from 24-87 weeks in accordance with the mentioned pathophysiological data. In the literature, most studies present a mean effect duration of 6-10 months and a mean re-injection time after 6-9 months (21). The mean re-injection period of our population was 84

(55-154) weeks. In our study, we detected that NB patients benefited for a shorter time period (32 weeks) and required multiple injections (55%) more than LUTD patients (87 weeks, 23%, respectively). There is a lack of literature on the cause of this difference in effect duration between NB and LUTD patients. LUTD patients have a disorder which is caused by the maturation delay of detrusor function. In our perspective, onabotulinum-A injection provides a period in LUTD patients to achieve detrusor function maturation and establish a better bladder-sphincter coordination in the absence of evident neurologic origin (5). This fact could lead to a more durable result as the bladder-sphincter dyssynergia plays a principal role in the pathophysiology of non-NB overactivity. However, NB patients have a permanent congenital structural disease, which causes the formation of hypertrophic or hyperactive detrusor muscle fibers. The provoked bladder wall ischemia and the fibroproliferative changes lead to lower compliance of the bladder (1,22). These changes in the bladder wall can lead to a decreased response to the administration of BTx-A injection (20). Also, Compérat et al. (23) showed that the bladder wall structure was different between BTx injection responder and non-responder patients. In fact, minor fibrosis was found in the bladder wall of responder patients. Since we don't have histological evaluation, we can just link our findings of difference between NB and LUTD patients to the possible relationship between the clinical response (duration of well-being and number of injections) and the degree of fibrosis in the bladder wall. Antibody levels before intervention may be another possible explanation (24). However, neither ours nor the studies in the literature investigated the difference between NB and LUTD patients in terms of antibody levels. As for the sphincter BTX-A injection, there are a limited number of studies in the literature. Previous studies on the sphincter BTx injection reported improvement rates in voiding and urodynamic parameters as 45-77%, and 40%, respectively (25,26). In our study, clinical improvement was observed in 75% (24/32) of all patients. Moreover, the mean follow-up was 30.1±5.8 months and decrease in DVISS and QoL scores were significant. One must acknowledge that the mean time to effect was 2 (0-4) weeks in both groups and it is measured at the beginning of the clinical improvement and it is in accordance with the previous studies (25,26).

The onabotulinum-A injection is regarded minimally invasive, but not without complications. Previous studies have mentioned UTI (4-29%) and urinary retention (4%) as the most encountered postoperative complications (13,21). In our study, none of the patients experienced UTI after the procedure. Only 1 episode of urinary retention and 1 episode of post-operative pain were recorded.

Our experience showed that the onabotulinum-A toxin injection is an effective alternative treatment options for NB and LUTD

patients who do not respond to first-line therapy. It is a minimal invasive procedure which can easily be repeated. The clinical and urodynamic outcomes are very satisfying, whereas the cost is far lower than that of bladder augmentation procedures. Although, it cannot replace the role of bladder reconstruction, particularly for NB patients, BTx injection has provided symptomatic relief in 75% that simply means to spare these children from more invasive major augmentation procedures.

Study Limitations

There are limitations in our study. Firstly, it was a retrospective study. Additionally, VUD was not performed in all patients post-operatively. VUD is a very painful and stressful examination, especially for the children. Due to being invasive, it has its possible adverse events. Therefore, in most of the cases, parents did not agree to their children to undergo another invasive examination only for academic purposes, once the clinical benefit was well established with the use of questionnaires. Actually, most of the previous studies revealed that objective assessment tools are most of the time in consistency with the subjective ones (21,23).

Conclusion

The results of our study show that BTx injection for children with NB and LUTD is effective and safe with the potential of saving a significant number of patients from further more invasive treatment. Although it was not surprising, this study was the first to show objectively that the effect of BTx injections in LUTD patients lasts longer and this population requires less number of interventions than the NB group. Our findings need to be verified by future studies with longer follow-up in a larger groups of patients with more detailed urodynamic evaluation.

Ethics

Ethics Committee Approval: The Local Ethics Committee (Hacettepe University Ethic Committee) approved the study protocol (decision number: GO-18/449, date: 15.05.2018).

Informed Consent: Patients were given detailed information about the procedure and informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S.D., S.T., Concept: A.C.B., E.C., H.S.D., S.T., Design: A.C.B., E.C., H.S.D., S.T., Data Collection or Processing: K.G., R.J., V.T., E.C., T.M., Analysis or Interpretation: A.C.B., E.C., H.S.D., S.T., Literature Search: K.G., R.J., V.T., T.M., H.S.D., Writing: K.G., V.T., T.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

References

1. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, Jørgensen TM, Rittig S, Walle JV, Yeung CK, Djurhuus JC. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006;176:314-324.

2. Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol 2015;14:720-732.

3. Nijman RJ. Neurogenic and non-neurogenic bladder dysfunction. Curr Opin Urol 2001;11:577-583.

4. Nijman RJ. Role of antimuscarinics in the treatment of nonneurogenic daytime urinary incontinence in children. Urology 2004;63:45-50.

5. Hoebeke P, De Caestecker K, Vande Walle J, Dehoorne J, Raes A, Verleyen P, Van Laecke E. The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol 2006;176:328-330; discussion 330-1.

6. Gamé X, Mouracade P, Chartier-Kastler E, Viehweger E, Moog R, Amarenco G, Denys P, De Seze M, Haab F, Karsenty G, Kerdraon J, Perrouin-Verbe B, Ruffion A, Soler JM, Saussine C. Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. J Pediatr Urol 2009;5:156-164.

7. Vricella GJ, Campigotto M, Coplen DE, Traxel EJ, Austin PF. Long-term efficacy and durability of botulinum-A toxin for refractory dysfunctional voiding in children. J Urol 2014;191:1586-1591.

8. Le HK, Cardona-Grau D, Chiang G. Evaluation and Long-term Management of Neurogenic Bladder in Spinal Dysraphism. Neoreviews 2019;20:e711-e724.

9. Dong M, Stenmark P. The Structure and Classification of Botulinum Toxins. Handb Exp Pharmacol 2021;263:11-33.

10. Radmayr C, Bogaert G, Dogan HS, Nijman JN, Silay MS, Stein R, Tekgül S; EAU Guidelines on Paediatric Urology 2020; 978-94-92671-07-3; presented at the EAU Annual Congress Amsterdam 2020.

11. Stein R, Bogaert G, Dogan HS, Hoen L, Kocvara R, Nijman RJM, Quaedackers J, Rawashdeh YF, Silay MS, Tekgul S, Radmayr C. EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part II operative management. Neurourol Urodyn 2020;39:498-506.

12. Hascoet J, Manunta A, Brochard C, Arnaud A, Damphousse M, Menard H, Kerdraon J, Journel H, Bonan I, Odent S, Fremond B, Siproudhis L, Gamé X, Peyronnet B; French Referral Network of Spina Bifida. Outcomes of intra-detrusor injections of botulinum toxin in patients with spina bifida: A systematic review. Neurourol Urodyn 2017;36:557-564.

13. Neel KF, Salem M, Soliman S. Total endoscopic management (TEM approach) of children with non-compliant neuropathic bladder: a preliminary report. J Pediatr Urol 2008;4:124-126.

14. Kajbafzadeh AM, Sharifi-Rad L, Ladi-Seyedian SS. Intravesical electromotive botulinum toxin type A administration for management of concomitant neuropathic bowel and bladder dysfunction in children. Int J Colorectal Dis 2016;31:1397-1399.

15. Hascoet J, Peyronnet B, Forin V, Baron M, Capon G, Prudhomme T, Allenet C, Tournier S, Maurin C, Cornu JN, Bouali O, Peycelon M, Arnaud A, Renaux-Petel M, Liard A, Karsenty G, Manunta A, Game X. Intradetrusor Injections of Botulinum Toxin Type A in Children With Spina Bifida: A Multicenter Study. Urology 2018;116:161-167.

16. Ringoir A, Dhondt B, De Bleser E, Van Laecke E, Everaert K, Groen LA, Hoebeke P, Spinoit AF. Intradetrusor onabotulinum-a toxin injections in children with therapy-resistant idiopathic detrusor overactivity. A retrospective study. J Pediatr Urol 2020;16:181.e1-181.e8.

17. Uçar M, Akgül AK, Parlak A, Yücel C, Kılıç N, Balkan E. Non-invasive evaluation of botulinum-A toxin treatment efficacy in children with refractory overactive bladder. Int Urol Nephrol 2018;50:1367-1373.

18. de Paiva A, Meunier FA, Molgó J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Proc Natl Acad Sci U S A 1999;96:3200-3205.

19. Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, Karsenty G, Schulte-Baukloh H, Schurch B, Wyndaele JJ; European Consensus Panel. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. Eur Urol 2009;55:100-119.

20. Rapp DE, Lucioni A, Bales GT. Botulinum toxin injection: a review of injection principles and protocols. Int Braz J Urol 2007;33:132-141.

21. Rohrsted M, Nordsten CB, Bagi P. Onabotulinum toxin a (botox®) in the treatment of neurogenic bladder overactivity. Nephrourol Mon 2012;4:437-442.

22. Ginsberg D. The epidemiology and pathophysiology of neurogenic bladder. Am J Manag Care 2013;19:s191-196.

23. Compérat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic features in the urinary bladder wall affected from neurogenic overactivity--a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. Eur Urol 2006;50:1058-1064.

24. Schulte-Baukloh H, Bigalke H, Miller K, Heine G, Pape D, Lehmann J, Knispel HH. Botulinum neurotoxin type A in urology: antibodies as a cause of therapy failure. Int J Urol 2008;15:407-415; discussion 415.

25. Georgopoulos P, Apostolidis A. Neurogenic voiding dysfunction. Curr Opin Urol 2017;27:300-306.

26. Aizawa N, Igawa Y. Pathophysiology of the underactive bladder. Investig Clin Urol 2017;58:S82-S89.