Case Report

Effectiveness of onabotulinumtoxin A for refractory overactive bladder with cough-associated detrusor overactivity

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Abbreviations & Acronyms
BTX-A = onabotulinumtoxin A
CADO = cough-associated detrusor overactivity
DO = detrusor overactivity
ICIQ-SF = International Consultation on Incontinence Questionnaire-Short Form
OAB = overactive bladder
Pabd = abdominal pressure
Pdet = detrusor pressure
Pves = vesical pressure
SUI = stress urinary incontinence
UDS = urodynamic study
UI = urinary incontinence
UUI = urge urinary incontinence

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Introduction: We report a case of refractory overactive bladder with cough-associated detrusor overactivity treated by onabotulinumtoxin A.
Case presentation: A 79-year-old woman who underwent mid-urethral sling surgery 8 years ago complained mainly of urinary incontinence following abdominal pressure. Various medicines to treat overactive bladder symptoms were ineffective. Cystometry revealed cough-associated detrusor overactivity. Onabotulinumtoxin A injections in her bladder improved subjective symptoms, and cough-associated detrusor overactivity disappeared on cystometry.
Conclusions: Onabotulinumtoxin A injection effectively resolved refractory overactive bladder with urgency urinary incontinence due to cough-associated detrusor overactivity.

Key words: cough-associated detrusor overactivity, onabotulinumtoxin A, refractory overactive bladder, urge urinary incontinence, urodynamic study.

Keynote message

CADO, detrusor overactivity appearing following abdominal pressure, is gradually being recognized, but its definition, mechanism, and treatment remain poorly discussed. We report a case of BTX-A effective in treating refractory overactive bladder with CADO. This report advances the understanding of CADO and may help in selecting future treatment options.

Introduction

BTX-A injection for refractory OAB is frequently effective for UUI.[1,2] CADO, a finding of UDS, is DO following Pabd and is clinically similar to SUI.[3] We report a patient effectively treated with BTX-A injection for refractory OAB and UI due to CADO after mid-urethral sling surgery.

Case presentation

A 79-year-old woman who underwent mid-urethral sling surgery 8 years ago visited our outpatient clinic complaining mainly of UI. She had no co-morbidities or past history except for hypertension. She had been taking anticholinergic agents (imidafenacin, fesoterodine) and β3-adrenoreceptor agonists (mirabegron, vibegron) in combination therapy because they were not effective as single agents. However, clinical symptoms of urinary urgency and incontinence with Pabd did not improve. Her OAB symptom score was 10 (Q1: 1, Q2: 1, Q3: 4, Q4: 4), and ICIQ-SF score was 16 (Q1: 4, Q2: 4; Q3: 8; touching water; leaks when coughing, sneezing, exercising). Her voiding diary indicated urinary frequency of 12 times/day and mean voided volume of 90 mL. Free uroflowmetry findings were within normal range (voiding volume: 203 mL, max flow rate:13.1 mL/s, average flow rate: 7.7 mL/s, residual volume: 0 mL). Cystometry (EDAP, LABORIE Urodynamic System, Portsmouth, NH, USA) using a 7Fr water-charged catheter showed first sensation of bladder filling, normal desire to void, and strong desire to void occurring at 71, 83, and 94 mL, respectively. DO did not occur

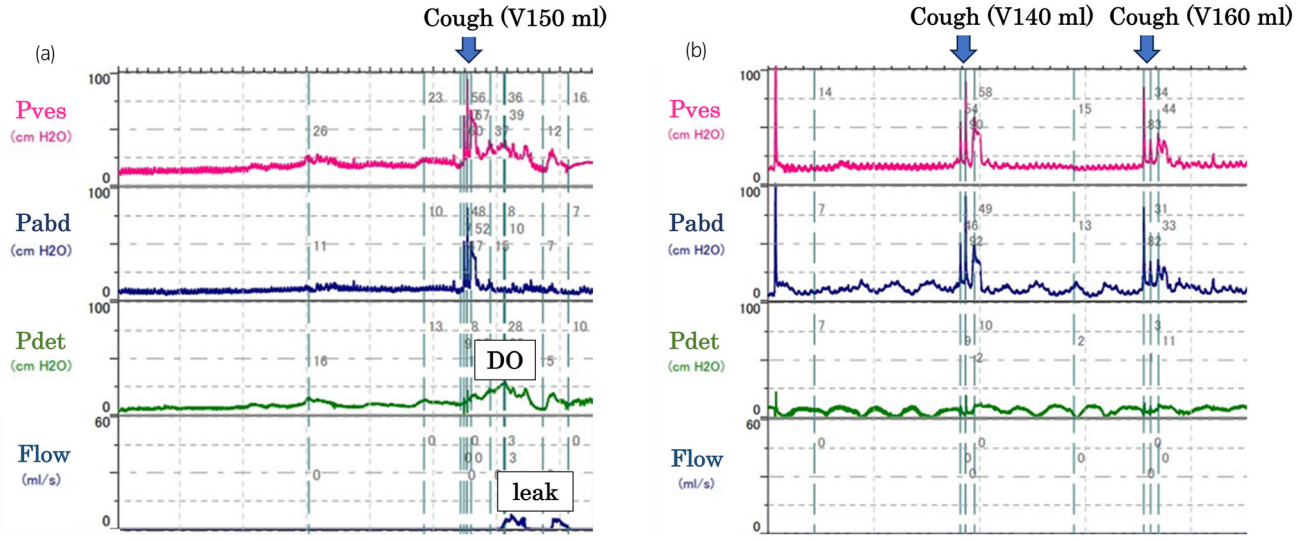

Fig. 1 UDS before and after BTX-A injection. (a) Cystometry before BTX-A injection. When 150 mL of water was injected into the bladder, DO occurred immediately following coughing, and UI was observed during DO. (b) Cystometry after BTX-A injection. No DO occurred after coughing when 160 mL of water was injected into the bladder.

during filling time but appeared after a cough test with a delay in Pabd that resulted in UI (Fig. 1a). She was considered to have CADO-induced UUI.

After the refractory OAB diagnosis, 100 units of BTX-A in 10 mL of physiological saline was injected. The posterior bladder wall was punctured with an injection needle, and 0.5 mL of BTX-A solution was injected into the bladder muscle layer at 20 locations. The 13-minute procedure was performed in the operating room under spinal anesthesia, and there were no surgical complications.

Two weeks post-BTX-A injection, her subjective symptoms improved. Two months post-operation, her OAB symptom score was 5 (Q1: 1, Q2: 1, Q3: 2, Q4: 1) and ICIQ-SF scores was 8 (Q1: 3, Q2: 2, Q3: 3, touching water). Voiding diaries showed urinary frequency of 8 times/day and mean voided volume of 180 mL. On cystometry, first sensation of bladder filling, normal desire to void, and strong desire to void occurred at 142, 166, and 235 mL, respectively. DO occurred at 235 mL, but no CADO was observed (Fig. 1b). According to the questionnaire, the effect of BTX-A remained unchanged for 9 months.

Discussion

BTX-A injections for refractory OAB are widely used in Japan thanks to insurance coverage since 2020.[2] Overseas reports of pre- and post-injection urodynamic studies objectively reported BTX-A efficacy, including increased maximum cystometric capacity and volume before the first appearance of DO.[4] The present report may be the first to show BTX-A efficacy for refractory OAB with CADO rather than for generalized DO.[4]

CADO can be confirmed by UDS. The International Continence Society first mentioned CADO at the 2016 Good Urodynamic Practices: "Cough associated DO is reported when the onset of the DO (with or without leakage) occurs immediately following the cough pressure peak."[3] Hogan *et al*. suggested diagnosing CADO only when the index cough precedes onset of the bladder contraction waveform with a <5-s latency.[5]

Clinically, CADO is similar to SUI, with the American Urological Association guidelines for SUI mentioning CADO as a differential diagnosis for SUI but not describing it in detail.[6] CADO incontinence differs from SUI by leakage occurring after a short delay rather than simultaneously with coughing. Predicting CADO from patients' complaints and symptoms alone is difficult. Our patient had residual UI after mid-urethral sling surgery for SUI. Preoperatively, she had mixed incontinence, with residual SUI also suspected. However, UDS revealed UI associated with CADO rather than Pabd itself, leading to the diagnosis and treatment of refractory OAB.

The mechanisms underlying CADO remain unknown. It is speculated that bladder neck expansion during Pabd and urine entering the proximal urethra may be caused by reflex bladder contractions (proximal urethra–spinal–bladder reflex).[7] This speculation may be one reason why closure of the urethra by mid-urethral sling surgery is sometimes effective for OAB. Even though our patient had undergone sling surgery, the effect of the surgery may not have been sufficient.

Although CADO is increasingly recognized, its characteristics remain unclear. One report of UDS in female patients with UI reported CADO prevalence of 2.2%,[8] whereas in another study of UDS in 1737 women with refractory OAB, 34.3% had a positive stress test and 38.7% had DO.[9] Those patients were tested for the diagnosis of refractory OAB, so a positive stress test may have indicated UI associated with CADO. We thus suggest that CADO is may often be included in refractory OAB, may be resistant to oral medications, and may likely be misdiagnosed as SUI.

No standard treatment exists for CADO. Sinha *et al*.[8] classified UDS results with CADO into four categories as incontinence associated with I: CADO (UUI), II: with cough (SUI), III: with both cough and CADO (mixed UI), and IV: with neither, and discussed the differences between them. For type II

CADO associated with SUI, Koonings *et al*. reported resolution of CADO after surgery for SUI.[7] For Type I cases, Sinha *et al*.[8] stated that surgery for SUI is inappropriate and management with a refractory OAB regimen is logical, but there are no reports of actual treatment. Although our patient complained of incontinence during Pabd, UI due to type I CADO indicated UUI. BTX-A injection for refractory OAB resolved her CADO and associated incontinence, confirming the speculation of Sinha *et al*. in actual clinical practice. More cases will be required to fully investigate the efficacy of this treatment.

Conclusion

We effectively used BTX-A injections into the bladder muscle layer to treat a patient with refractory OAB and UUI due to CADO. Clinicians should keep in mind that a patient with incontinence refractory to treatment may have UUI due to CADO, even if the patient's complaints are similar to those of SUI.

Author contributions

Chie Nakai: Conceptualization; data curation; writing – original draft. Kosei Miwa: Supervision; writing – review and editing. Akane Yamaguchi: Investigation; resources. Yasumichi Takeuchi: Investigation; resources. Masami Yamaguchi: Investigation; resources. Yasuhide Kitagawa: Supervision; writing – review and editing. Takuya Koie: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

This case report was approved by the Institutional Review Board of Japanese Red Cross Gifu Hospital (No. I20090901).

Informed consent

Not applicable.

Registry and the Registration No. of the study/trial

Not applicable.

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