Case Report

Focal arm weakness following intradetrusor botulinum toxin administration in spinal cord injury: Report of two cases

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Context: Outpatient Spinal Cord Injury follow-up practice

Findings: We present two cases of individuals with tetraplegia who experienced proximal arm weakness temporally related to the administration of intradetrusor onabotulinumtoxinA without other systemic effects. This arm weakness lasted approximately three months in both cases, whereas the effect of the toxin on the bladder lasted for over six months. In one of the cases, the pattern of proximal arm weakness after intravesicular botulinum toxin injection recurred after repeat injection.

Conclusion: These cases represent a previously unreported phenomenon of proximal focal weakness associated with the use of intradetrusor chemodenervation. Possible mechanisms for these cases are discussed.

Keywords: Detrusor overactivity, Neurogenic bladder, Chemodenervation, Botulinum toxin, Arm weakness

Introduction

Botulinum toxin is frequently used for managing spasticity, movement disorders, and a variety of other conditions.¹ In recent years, the use of botulinum toxin to treat (bladder) detrusor overactivity resistant to anticholinergic medications has grown significantly because the procedure is minimally invasive and offers high rates of symptomatic improvement.^{2,3} Success rates from this application (including both subjective patient symptom improvement scores and urodynamic measures) are consistently reported as high.^{3,4} The majority of known side effects of intradetrusor botulinum toxin administration are local in nature (i.e. injection site pain, procedure-related urinary tract infection, hematuria, or increased post-void residuals necessitating new intermittent catheterization).⁵ Less frequently, systemic side effects including double vision/ptosis, dysphagia, and generalized weakness have been

reported.⁶ Analysis of these cases reveals very little in regards to the risk factors or mechanism related to these effects.⁷

The cases described in this report deal with post intradetrusor botulinum toxin development of focal weakness manifested by bilateral shoulder/triceps weakness without other muscular weakness. To our knowledge, these are the only reported cases of focal rather than systemic weakness secondary to intradetrusor botulinum toxin injection therapy.

Case 1

The patient is a 66-year-old man with C7 American Spinal Injury Association Impairment Scale (AIS) D tetraplegia from a remote motor vehicle accident. At baseline, he had the following bilateral arm strength on manual muscle testing:⁸ deltoid, biceps and wrist extension muscle grade 5, triceps muscle grade 4, flexor digitorum profundus middle finger (FDPm) and abductor digiti minimi (ADM) muscle grade 5. Over a period of 16 months, the patient underwent three administrations of intradetrusor onabotulinumtoxin A, 300 units (U) each, for detrusor overactivity. Following

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the first administration, the patient developed bilateral arm weakness such that he was unable to lift his arms above shoulder level. This history was provided by the patient retrospectively. The patient had improvement of his urologic symptoms, whereby his incontinence resolved completely for over nine months. His shoulder weakness resolved gradually over three to four months. The patient did not associate his shoulder symptoms with the intradetrusor botulinum toxin injection. He did not report the symptom to any of his treating physicians at the time. Ten months following the first procedure, the patient underwent repeat intradetrusor onabotulinumtoxin A (300 U) administration, again with urologic symptomatic improvement but rapid onset of similar shoulder weakness. After this injection, the patient specifically stated that he was unable to hold his rifle to shoot clay pigeons, one of his pastimes. The shoulder weakness again resolved gradually at three months, with resolution again multiple months prior to re-emergence of urologic symptoms. A third administration was performed six months after this, again with onset of shoulder weakness. It was only at this point that the link between the bladder injections and the shoulder injections was made. Examination of his right shoulder one month after the third procedure revealed bilateral shoulder external rotation and abduction weakness (muscle grade 4) without pain. His biceps and wrist extensors remained normal in strength. There was no pain on palpation of structures of the shoulder. The patient had no other notable changes in muscular strength or other side effects. Of note, the patient had previously received multiple rounds of onabotulinumtoxin A and rimabotulinumtoxin B intramuscularly for lower extremity spasticity without any type of side effects, including one administration of 20,000 U of rimabotulinumtoxin B soon after his second intradetrusor injection procedure.

Case 2

The patient is a 46-year-old male with C6 AIS C tetraplegia from a remote motor vehicle accident. At baseline he had the following upper extremity motor examination: biceps muscle grade 5 bilaterally, wrist extensors muscle grade 5 bilaterally, triceps muscle grade 1 right 2 left, FDPm muscle grade 0 right 1 left, ADM muscle grade 0 right 1 left. The patient underwent a single administration (300 U) of intradetrusor onabotulinumtoxin A for detrusor overactivity. Approximately two weeks after the procedure, the patient called to report development of severe functional weakness manifested as inability to perform transfers independently. Examination revealed full strength in the biceps and

wrist extensors (5/5), but the patient had decreased triceps strength (1 bilaterally) such that he was unable to lock his elbows into extension (previously his left triceps strength of 2 was enough to allow him to lock his elbow in extension and allow for transfer). This resulted in a significant functional impairment for the patient, whereby he was unable to transfer to and from his wheelchair. The patient reported gradual resolution of this weakness over a period of months, but noted at follow up eight months after injection that his strength was still not back to his prior-to-procedure level.

Discussion

These cases illustrate the development of localized, proximal, weakness following intradetrusor botulinum toxin administration. This unique presentation raises a number of questions regarding the mechanism of action of botulinum toxin and the pathophysiology of its side effects.

Botulinum toxin is a potent neurotoxin originally derived from the bacterium *Clostridium botulinum*.⁹ The toxin's best-known mechanism of action is to inhibit acetylcholine release into the neuromuscular junction, thereby blocking neuromuscular signal transmission and causing sustained paralysis.^{9,10} It was first reported in 1996 for the treatment of urologic disorders by Schurch *et al.* and is now used frequently in the treatment of detrusor overactivity.^{10,11} Recent research points to larger neural effects of botulinum toxin on the bladder apart from its effects on acetylcholine release. These include inhibition of multiple neurotransmitters and down-regulation of purinergic and capsaicin receptors on afferent neurons.^{9,10} Additional postulated mechanisms include decreased axonal sprouting in botulinum toxin treated smooth muscle as compared to striated muscle, as well as decreased levels of the sensory receptors P2X3 and/or TRPV1.^{12–14}

The high selectivity and tight local binding of botulinum toxin contribute to the high success rate of treatment, durable effect, and low frequency of side effects.^{10,15} Even so, these cases show the potential for systemic side effects related to botulinum toxin therapy. There are also many other case reports describing occurrences of generalized symptoms manifesting as weakness, functional limitations, and speech and respiratory difficulties following botulinum toxin administration.^{1,3,15} These symptoms have been seen after both intradetrusor and peripheral intramuscular administration.

One of the main theories behind generalized weakness following botulinum toxin injection is systemic spread

through the bloodstream, which is a widely known risk whenever the toxin is injected into muscles. Wyndaele *et al.* reported two cases of generalized muscle weakness following intradetrusor botulinum toxin injection, notable for the procedures having a minimal effect on bladder spasticity. The authors hypothesized that the toxin spread to the systemic circulation because there was poor local toxin binding.¹⁵ However, our cases, along with others, feature side effects occurring after good bladder symptom response.^{1-3,15}

Retrograde axonal transport is another possible mechanism of diffuse botulinum toxin spread. Radioactive-labeled botulinum toxin has been shown to migrate towards the spinal cord.¹⁶ However, this process is thought to be very slow, to the point that toxin is inactivated by the time it reaches the spinal cord.⁵ Some alternate mechanisms may also be involved. Electromyography of muscles distant from botulinum toxin administration sites have shown there is indeed a generalized effect on muscles throughout the body from localized botulinum toxin injection, even in patients without weakness.¹⁷

That botulinum toxin dose is a risk factor for systemic side effect development remains controversial.¹⁸ Borodic *et al.* showed local spread of botulinum toxin is dose dependent.¹⁹ However, Marzi *et al.* showed that side effects occurred in patients that received both low and high doses.²⁰ In our cases, the patients received 300 U onabotulinumtoxin A at each treatment, which is a relatively low dose compared to dosages often used in skeletal muscle.¹

The question of why the presentation in these two cases was focal and not systemic remains puzzling especially in case one where baseline motor strength was greater. There have only been a small number of reported cases of focal and/or asymmetric symptoms. Joshi detailed the case of generalized weakness with particularly severe weakness of the left wrist flexors following intramuscular botulinum toxin administration.²¹ Another case noted onset of contralateral weakness following administration to the upper extremity of a patient with hemiparesis, though given the hemiparesis it is unclear whether this is localized or systemic spread.²² Some cases of contralateral limb weakness in hemiparetic patients without systemic side effects have additionally been reported.²³ However, none of these cases involved intradetrusor botulinum toxin administration.

The patient described in the first case had a history of tolerating previous lower limb skeletal muscle botulinum toxin injections. This raises the question of differential susceptibility to side effects when botulinum toxin is injected into skeletal muscle versus the smooth

muscle of the bladder. Motor recovery following botulinum toxin takes two to three months in striated muscle, whereas in smooth muscle this can take six to twelve months.¹⁵ There is also an apparent difference on a biochemical level.⁵ As such, it has been postulated that systemic effects of botulinum toxin are more common following smooth muscle administration, but the literature overall is not conclusive.³ Multiple reports detail the development of generalized side effects in patients who had previously tolerated other botulinum toxin treatments. However, in those cases the symptoms had not been reproducible as in our case.¹ Indeed, one of the most compelling features of the first case was the reproducibility of symptoms, which is unique to the published literature.

These reports illustrate the challenge of recognizing focal weakness as a possible side effect of botulinum toxin therapy. In the first case, shoulder weakness was not recognized as related to botulinum toxin until after the third intradetrusor botulinum toxin administration. During that time, the patient underwent workup for cervical spine related pathology and was set to receive cervical epidural injections in hopes of treating in his symptoms. Had the connection between the shoulder weakness and botulinum toxin therapy not been made, the patient may have avoided this additional procedure.

The responses to intradetrusor botulinum toxin administration seen in here represent unique presentations of proximal focal weakness. It should be pointed out that incidents like these are extremely uncommon. Nonetheless, while botulinum toxin has a longstanding record of safety and efficacy in treating neurogenic bladder, distant and focal parietic symptoms as are possible and can have serious functional implications.

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Conflicts of interest The authors declare no conflicts of interest.

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