



# Atypical hypersensitivity reaction to botulinum toxin injection: a case report

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**Edited by:**  
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**Keywords:**  
Botox  
Chronic headache  
Anaphylaxis  
Drug-related side effects and adverse reactions

### Abstract

Botulinum toxin type A (BTA) injection, marketed as BOTOX, is commonly used as a treatment for a variety of clinical indications and is widely viewed as safe, effective and largely devoid of serious side effects. Anaphylactic reactions to BTA are typically unheard of in the scientific literature. BOTOX is approved by the Food and Drug Administration for the treatment of cervical dystonia and prophylaxis for chronic migraines. This case report documents a unique instance of allergic reaction to BTA in a 29-year-old woman with cervicogenic headache and cervical dystonia who reported immediate flushing, light-headedness and nausea after receiving BTA injections.

Submitted: June 14, 2023  
Accepted: June 21, 2023  
Published online:



## Introduction

Cervicogenic headache is characterized as unilateral pain that starts in the neck and is referred from bony structures or soft tissues of the neck to the head or face.<sup>1</sup> It is a common chronic and recurrent headache that usually starts following neck movement and is often accompanied by reduced range of motion (ROM) of the neck.

The diagnostic criteria for cervicogenic headache necessitate that the source of the pain be perceived in the neck and refer to the head or face, confirmation of the same as evidenced by the termination of a headache following diagnostic blockade of a cervical structure, and resolution of pain perception within 3 months after treatment.<sup>2,5</sup>

Botulinum toxin type A (BTA) is used clinically for several conditions, including migraine headaches.<sup>6</sup> Disturbed neuromuscular function forms the basis behind the treatment of cervicogenic headache with BTA.<sup>7</sup> Botulinum toxin type A blocks the release of acetylcholine at the neuromuscular junction and may partially paralyze muscles for a few months.<sup>8-11</sup>

Cervical dystonia is a disabling movement disorder, denoted by involuntary and painful head posturing. Botulinum toxin type A is considered the first-line therapy for this condition.

Anaphylactic reactions to BTA are typically unheard of with only three prior cases reported in the literature. Herein, we describe a unique case of allergic reaction to BTA for treatment of cervicogenic headache and cervical dystonia.

## Case Description

A 29-year-old female with a history of chronic migraines and cervicogenic headache, seasonal allergies, allergies to bee venom and intermittent asthma presented for administration of botulinum toxin injections (reconstituted with 0.9% normal saline to a concentration of 100 U/1cc) for treatment of cervicogenic headaches and cervical dystonia. The patient reported a 15-year history of chronic headaches, which had worsened the previous six months prompting referral to physiatry for further management. During these six months, the patient reported increasing headache frequency (from 2-3 headaches per week to daily), duration (from 2-3 days per headache episode to headaches lasting up to 15 days), intensity (average pain rating increased from 2/10 to 8/10), and increased days she called in sick from work (from 1 day per month to

6-7 days per month). The headaches were described as a unilateral throbbing pain around her eyes in addition to an ipsilateral dull pain involving the frontal, temporal and occipital areas of the head radiating down the posterior neck. She reported alternating lateralization of her headaches. Associated symptoms included dizziness, sensitivity to light, loss of vision and visual disturbances, nausea and vomiting. She did not report any precipitating factors for her headaches.

She had attempted multimodal pain control with acetaminophen, aspirin, multiple non-steroidal inflammatory medications, gentle mobilization and stretching of the cervical spine, application of heat and ice to the posterior neck resulting in only mild relief. Six weeks prior to her visit, she had received a bilateral greater occipital nerve block, 4 ml total of 1% lidocaine. This procedure provided her mild to moderate relief, though she continued to report debilitating daily headaches.

Upon physical examination, the patient was noted to have significantly reduced passive and active range of motion of the cervical spine, with reduced cervical rotation of 60 degrees to the left, 50 degrees to the right, side bending of 50 degrees to the left and 70 degrees to the right. At rest the patient was noted to have a head tilt to the left with cervical extension. Tinel's sign was positive for greater occipital nerve irritation bilaterally, with the left side eliciting a greater pain than the right. Significant tenderness to palpation was also noted along the cervical paraspinal muscles, trapezius muscles (left>right), and levator scapulae, bilaterally. Mild to moderate muscle spasms were noted in the same regions.

She received BTA injections to the frontalis (20 units divided into four sites), procerus (5 units), left temporalis (20 units), left obliquus capitis inferior (25 units), left sternocleidomastoid (10 units), left trapezius (30 units), and left levator scapulae muscle (15 units). She reported immediate flushing, light-headedness and nausea after the first injection, which slowly worsened with each subsequent injection performed. Upon attempted injection of the left levator scapulae muscle, the patient requested to cease receiving further injections. Immediately after cessation of injections, the patient then experienced vomiting. A total of 200 units of botulinum toxin was planned for injection, but only 125 units were used.

Upon returning home, the patient reported continued symptoms of nausea and vomiting throughout the day



despite treatment with sublingual ondansetron HCl. After 12 hours of ongoing symptoms, the patient reported taking cetirizine HCl 10 mg and diphenhydramine HCl 25 mg, which improved her symptoms. Her symptoms continued through the next ten days, improving intermittently with alternating the above antihistamine administration. The patient reported a complete resolution of her symptoms after 10 days.

## Discussion

This is the first reported case, to our knowledge, describing a type I hypersensitivity reaction following the administration of BTA injections given at what is commonly considered to be a standard dose for adults with cervicogenic headache and cervical dystonia. In this case, improvement of symptoms with antihistamine administration points to the likelihood of an abnormal allergic response to BTA injection.

Anaphylaxis is characterized as the acute onset of an illness involving the skin, mucosal tissue, or both and at least one of the following: (1) Respiratory compromise or (2) Reduced blood pressure or associated symptoms and signs of end-organ dysfunction.<sup>12</sup>

Botulinum toxin type A has undergone rigorous clinical evaluation in numerous randomized controlled trials and open-label studies across a broad range of clinical indications with the majority of studies reporting no serious side effects. However, a recent Cochrane review, which included 1,144 participants with cervical dystonia over 9 RCTs did report that people treated with BTA are at an increased risk of developing dysphagia, neck weakness and diffuse weakness or tiredness.<sup>13</sup>

A few cases of acute hypersensitivity reactions following BTA administration have been reported in the scientific literature following treatment with BTA for various clinical indications.

Aggarwal et al.<sup>14</sup> describe administering 90 units of BTA (reconstituted in normal saline) into the lower esophageal sphincter of a 47-year-old male patient during an endoscopy procedure for the treatment of achalasia cardia that resulted in immediate swelling of the eyes and face, malignant hypertension and tachycardia. An emergency cricothyroidotomy was performed along with administration of 100 mg of hydrocortisone IV and 50 mg of diphenhydramine IV. Epinephrine was avoided due to the patient's high blood pressure and tachycardia. The patient was then transferred to the medical intensive care

unit and was ultimately discharged in stable condition.<sup>14</sup>

Moon et al.<sup>15</sup> describe a case of unusual life-threatening reactions minutes after BTA injection into the masseter muscle of a 35-year-old female patient presenting for a cosmetic procedure. Approximately 5 minutes after 25 units of BTA were injected, the patient developed severe rhinorrhea accompanying nasal obstruction and swollen eyes, suggestive of angioedema. She also developed concomitant weals on her extremities in addition to experiencing mild dyspnea and chest tightness during the attack. Intramuscular injections of epinephrine 1 mg along with chlorpheniramine 4 mg, diphenylpyraline 3 mg and dexamethasone disodium phosphate 5 mg were immediately administered. The nasal obstruction and rhinorrhea subsided approximately 1 hour after treatment, but the swelling on the periocular areas lasted for 4 hours.<sup>15</sup>

Careta et al.<sup>16</sup> describe the development of urticarial plaques proximal to the injection site in a 44-year-old woman who presented for 32 IUs of BTA injection to the upper face to treat dynamic wrinkles. The authors administered systemic corticosteroids and antihistamines, noting gradual improvement 6 hours later.

Li et al.<sup>17</sup> described the first fatality associated with a BOTOX-lidocaine mixture given to a woman for chronic neck and back pain. However, because the BOTOX was reconstituted in 1% lidocaine, it was determined that the anaphylaxis may have been due to the lidocaine and not the BTA.

## Conclusion

Treatment with BTA is widely viewed as safe, effective and largely devoid of serious side effects. This case describes an extremely rare circumstance of type I hypersensitivity reaction following BTA injection. Consideration of prophylactic administration of antihistamines or other immunosuppressive agents such as steroids may be helpful in preventing the incidence of future hypersensitivity reactions to BOTOX.

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