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Contemporary Review

Contemporary Review and Case Report of Botulinum Resistance in Facial Synkinesis

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Background: Botulinum resistance poses significant treatment challenges for both patients and healthcare practitioners. We first present a case highlighting botulinum resistance in a patient who failed to respond to alternative formulations but who responded remarkably to incobotulinum toxinA, an identical toxin free of complexing proteins. Secondly, we provide a treatment algorithm and a review of the literature detailing clinical and immunochemical botulinum resistance.

Results: Patients with botulinum resistance show a predisposition to failure on subsequent injections and possess a propensity toward neutralizing and non-neutralizing antibody development. The mechanisms of resistance are not entirely understood but thought to be secondary to an immunologic response. Risk factors for resistance include higher botulinum doses, more frequent injections, and high total lifetime dosage. Patients may still respond to other botulinum formulations or subtypes; however, this effect may be temporary.

Conclusion: This case report describes a patient who responded to incobotulinum toxinA after failing treatment with the identical toxin compounded with buffer proteins, ultimately supporting the possibility of immune-mediated resistance to the surrounding proteins and not the toxin itself. Often, impending treatment resistance is preceded by a poor or limited clinical response. Antibody testing is not indicated because it is neither sensitive nor specific and does not change clinical practice. Initially, higher doses of botulinum may overcome resistance without increasing treatment frequency, and side effects are far less common in those with clinical resistance. If higher dosages fail to produce a response, alternative botulinum formulations or subtypes can be considered.

Key Words: Facial nerve, synkinesis, botulinum resistance.

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INTRODUCTION

Facial synkinesis is the involuntary contraction of muscles in combination with voluntary movements that develop after facial denervation or nerve injury. The treatment of the disorder is predominantly physical therapy and chemodenervation, with select adjunct surgical procedures.1–4 There are several agents used for chemodenervation, although all contain the clostridium botulinum neurotoxin. The toxin enters the neuromuscular junction and prevents vesicular release of acetylcholine from the presynaptic terminal into the synaptic cleft through irreversible inhibition of the soluble NSF attachment protein (SNARE) complex.9–13 This precludes the muscular action potential and results in flaccid paralysis.

Botulinum neurotoxin was approved by the Food and Drug Administration in 1989 and has been used successfully for a variety of clinical disorders.14,15 It is indicated for detrusor hyperactivity, chronic migraines, limb spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm, and strabismus. It is regularly employed for cosmetic procedures and facial synkinesis.14–18 However, there are reports within the literature of botulinum resistance, particularly in patients with repetitive or frequent administration, high-dose injections, and large lifetime doses.10–12,19–24 Although the mechanism of resistance is not well understood, it is thought to result from immunogenic antibody development.9,11,10,20,25 There is, however, conflicting evidence because patients found with botulinum antibodies respond unpredictably to the neurotoxic effects and, contrarily, patients without identified antibodies may still demonstrate clinical resistance.19

We first describe a patient with longstanding facial synkinesis who initially received significant improvement to onabotulinum toxinA but subsequently developed resistance. After trialing different formulations of available botulinum therapy, the patient responded remarkably to incobotulinum toxinA, an identical toxin free of...
complexing proteins. We here discuss the difficult management options prior to and after the development of resistance, as well as the response to alternative botulinum formulations, and then provide a review of the literature detailing clinical and immunochemical botulinum resistance.

Case Description

A 53-year-old woman with a history of left hemifacial weakness and subsequent facial dyskinesis due to Ramsay Hunt syndrome was treated at a tertiary care center from November 2011 through February 2018. The patient initially developed left-sided facial paresis, graded House-Brackman IV of VI after a vesicular eruption on the associated side of the face. The patient was treated with three courses of oral steroids without benefit and ultimately developed progressive synkinesis over the next 4 months following the facial injury.

At the time of synkinesis onset, the patient developed midface tightening, oral commissure hyperkinesia, cheek biting, decreased oral competence, narrowing of palpebral fissure, and significant discomfort and pain. Despite rigorous facial therapy, the patient continued to have significant symptoms and 7 months after developing facial dyskinesis was referred for botulinum therapy using onabotulinum toxinA. At initiation of treatment, the patient was determined to have a Sunny Brook Facial Grading Scale composite score of 23 (resting symmetry 15, voluntary movement 48, and synkinesis total 10). The patient’s general facial strength greatly improved, which complicated the synkinesia; however, the patient’s Sunny Brook score also improved to a score of 50 after multiple botulinum toxin treatment sessions.

From 2011 until 2018, the patient underwent five surgeries and 32 treatment sessions, which were on average every 86 days with a total treatment time of 88.8 months. A summary of disease onset and treatments are shown in Figure 1. After surgical attention to the eye and neck, the patient’s predominant complaints were midface tightness and hyperkinesia, oculo-oral synkinesis, and hypertonic-induced pain and discomfort.

The patient’s first treatment included 13.75 units of botulinum toxin distributed throughout the upper and lower face and neck. The total dose fluctuated during the course, with two peaks at approximately 2 years and 3 years into therapy; however, the patient received progressively less therapeutic relief, with a total dosage of 70 units. Even at higher doses, the therapeutic effects of onabotulinum toxinA were marginal and lasted less than a month, with toxin administration of 22.5 units in the upper face, 37.5 units in the midface, and 10 units in the lower face.

Given this treatment failure, the chemodenervation agent was changed to abobotulinum (Dysport, Galderma Laboratories, Fort Worth, TX), which yielded minimal results. Subsequently, incobotulinum toxinA (Xeomin, Merz Aesthetics, Raleigh, NC) resulted in a robust response. The patient experienced significant reduction of tightness in the midface and central cheek as well as greatly improved ocular opening and reduced visual field obstruction. This improved efficacy has lasted over the three treatment sessions. Treatment photographs are shown in Figure 2.

DISCUSSION

Facial synkinesis is a difficult disorder to treat, often requiring both a combined medical and surgical approach. Chemodenervation is successful in providing temporary relief and improved quality of life by taking advantage of clostridium botulinum’s distinct neurotoxic effects.

Fig. 1. Timeline and progression to botulinum resistance in facial synkinesis. BT = botulinum toxin; PT = physical therapy; SAQ = Synkinesis Assessment Questionnaire. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
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but lacks associated buffer proteins.30,31 tulinum toxinA, which contains the identical neurotoxin resistant, the patient subsequently responded to incobo-
response and dependable relief. After becoming clinically dosages with decreased effect after many years of herein. Our patient slowly required increasing onabotuli-
molecular weight and bacterial origin, and that creates a improvement with incobotulinum, a formulation derived of solution proteins, and excipients. In a cohort of patients with sec-
molecular weight and bacterial origin, and that creates a complex with nonclostridial proteins.9–12 Clinical formu-
lations also vary based on the clostridial strain, composite proteins, and excipients. In a cohort of patients with sec-
nder resistance, Barnes et al. found 69% of patients without antibodies and 31% with antibodies to the toxin A or its complex.19 Other studies report the presence of antibodies in less than 5% of patients and additionally in those without overt signs of clinical resistance.11,20,22,29

It is thought that patients with clinical resistance develop neutralizing antibodies that block the toxin effects, whereas those without resistance may develop non-neutralizing antibodies that do not target the effector site.12 It is reasonable that patients with secondary treat-
formulations or subtypes. After treatment failure with botulinum toxinA, patients have been reported to respond to other strains of botulinum, such as botulinum toxinB.10,11,13,19,35–37 This supplementary response, however, may only be transient, with symptom improvement for several treatment sessions. Additionally, the required effective dose for botulinum toxinB is much greater than that of type A, with a shorter duration of effect. Most patients will experience more significant dose-dependent side effects, including initial and persistent injection site pain, xerostomia, dysphagia, lack of accommodation, conjunctival irritation, reduced sweating, heartburn, constipation, urinary retention, and intranasal drying.9,19,35

This case report describes a patient who responded to incobotulinum toxinA after failing treatment with the identical toxin compounded with buffer proteins, ultimately supporting the possibility of immune-mediated resistance to the surrounding proteins and not the toxin itself. This may represent continued botulinum efficacy, bypassing the development of autoantibodies to the compexing proteins present in other formulations. Fortunately, secondary treatment failure is not common and only occurred in the patient described here compared to the large cohort of over 100 patients who we treat on 3-month intervals. It may be that our patient developed
treatment failure due to the frequent injections, with 10 of 32 injections occurring within 3 months and two within 1 month of each other, as well as the larger botulinum amounts necessary for treatment effect compared to more typical doses utilized for facial synkinesis (average = 40 units; lifetime = 896 units).

We recommend following patients clinically, and if concern with impending resistance arises, to not aggressively inject more often but to reassure and maximize therapy at higher dose treatments in at least 3-month increments. Understanding the patient’s disease course is also important because patients will not improve in up to 10% of treatments sessions but will on subsequent injections. Impending resistance may be overcome with increased doses and close monitoring of side effects, which are overall less significant in those who are clinically resistant. Select dynamic or static facial reanimation surgical procedures can also be offered as indicated. We do not recommend testing for antibodies to determine resistance; this is a clinical assessment, and antibody testing is neither sensitive nor specific and currently does not change practice. In combination with patient preference and response, a trial of different botulinum A formulations may be attempted given the complex nature of resistance. If these efforts continue to provide limited improvement, botulinum toxin B formulations may be trialed. At this time, the patient should also be counseled that improved effect may be transient over several sessions and not likely a long-term solution, and that there may be a higher rate of side effects and injection site pain. Figure 3 illustrates a recommended treatment algorithm.

The overall cost varies; depends on the regional market; and incorporates both fixed and variable costs such as provider expenses, frequency of injections, and medical and social services. Unfortunately, stakeholders have driven many of the existing cost-comparative studies, and the results should be considered accordingly. Generally, abobotulinum is the most affordable; however, incobotulinum was found to be the most cost-effective in one study. Additionally, each formulation is aliquoted into different doses, and treatment can be tailored on an individual basis while minimizing waste and reducing overall cost.

We are limited because this is a case report in which we did not test for botulinum antibodies and did not assess botulinum toxin type B response. In reviewing the literature, the mechanism of botulinum resistance remains unknown, although it is likely secondary to antibody-induced immunity with intertwining and complex interactions. Evidence in other systemic disease processes supports that immunogenic therapies may be administered in different frequencies and doses to minimize the consequences, such as in patient’s undergoing anti-interferon (IFN) for multiple sclerosis, which shows a decreased likelihood of antibody development in weekly therapy compared to more frequent treatments at lower dosages. It would be interesting to determine the optimal dosing and frequency of administration for botulinum therapy to minimize the risk of antibody formation and thus decrease the risk of resistance. In the future, larger studies, perhaps multi-institutional, of this uncommon phenomenon may provide statistical power to determine a precise mechanism of botulinum resistance, whether antibodies are truly associated with the development of secondary resistance, and whether antibody identification could complement clinical management. Finally, patients who are more likely to develop resistance include those with high treatment doses, frequent injections, and a high lifetime dose. It would be interesting to establish if those who received botulinum therapy for cosmetic purposes such as alleviation of facial rhytids are at an increased predisposition to botulinum resistance.

CONCLUSION

Patients who require frequent botulinum injections at high doses are at increased risk of developing resistance, which is a clinical diagnosis. At this time, antibody testing does not provide any additional value. Patients may fail to respond to an individual therapy session, and repeat injections with close monitoring are indicated. However, if continued therapy provides little to no response, then clinical resistance may be overcome with increased dosages at standard 3-month frequencies, and trials of alternative botulinum formulations or subtypes may be considered.