Case report

Botulinum toxin injections associated with suspected myasthenia gravis: An underappreciated cause of MG-like clinical presentation

Anna Rostedt Punga, Maarika Liik*

Department of Neuroscience, Clinical Neurophysiology, Uppsala University, Uppsala, Sweden

Abstract

Introduction: The application of botulinum toxin type A (BoNTA) is accelerating, and this includes the uncontrolled cosmetic use of the BoNTA. Diffusion of BoNTA can disturb neuromuscular transmission in several surrounding and distant muscles and result in clinical manifestations similar to myasthenia gravis (MG).

Case presentations: We report two cases of patients referred for neurophysiological evaluation of suspected MG. A 55-year-old female who experienced dysphagia, dysarthria, right-sided ptosis, and neck extensor muscle weakness; and a 46-year-old male who presented with episodic double vision and right-sided ptosis. Both had the history of previous BoNTA use for cosmetic purposes and for the treatment of migraine before the presentation of their symptoms. In both cases examination revealed normal RNS, quite remarkably increased jitter, and signs of denervation and reinnervation in muscles surrounding the injection sites. After extensive neurophysiological evaluations, the primary cause of their symptoms was found to be related to previous BoNTA injections rather than a primary neuromuscular transmission disorder. It could also be concluded that patients do not automatically inform their physicians about cosmetic BoNTA use and they may not be aware of the potential risks associated with BoNTA therapy.

Conclusions: The presented cases illustrate the neurophysiological findings in two patients with suspected MG after the use of BoNTA and emphasize the importance of inquiring about previous BoNTA injections and highlight that it is essential that patients are informed about possible side effects of BoNTA therapy.

© 2020 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The use of botulinum toxin type A (BoNTA) for various indications is growing in the areas of neurology and dermatology. Wrinkle corrections through injections of botulinum toxin A (BoNTA) in the facial muscles include the rather uncontrolled cosmetic use during so called “botox parties”. Diffusion of BoNTA can disturb neuromuscular transmission in facial/extraocular muscles and result in false positive electrodiagnostic findings regarding neuromuscular transmission disorders (Alimohammadi et al., 2014; Girlanda et al., 1996). We report two cases of patients referred for neurophysiological evaluation of suspected myasthenia gravis (MG). After extensive evaluations with electromyography (EMG), repetitive nerve stimulation (RNS) and single-fiber EMG using concentric EMG needle (CNE), the primary cause of their symptoms was found to be related to previous BoNTA injections rather than a primary neuromuscular transmission disorder.

2. Case reports

2.1. Case 1

A previously healthy 55-year-old female patient was referred for neurophysiological evaluation with the suspicion MG or bulbar amyotrophic lateral sclerosis (ALS). She experienced dysphagia of solid foods, slight dysarthria and right-sided ptosis, neck extensor muscle weakness and weight loss of 8 kg over a few weeks. No double vision or diurnal fluctuations were reported. Radiological evaluation of the hypopharynx and esophagus revealed abnormal movement of the epiglottis and slight aspiration, although an internal medicine physician found no signs of laryngeal disorder. Neurological examination was normal and serum AChR- and MuSK antibodies negative.
Electrophysiological studies one month after symptom onset revealed normal nerve conduction studies of both arms and legs and normal 3 Hz RNS (anconeus, deltoid, trapezius and nasalis muscles; Fig. 1a). The CMAP amplitudes were towards the lower end of the normal range, and did not increase after 20 s of maximal voluntary contraction (Table 1). Voluntary CNE of 10 potential pairs (the patient was not able to contract longer for the collection of more pairs) for both muscles revealed increased jitter (70%) and blockings (20%) in the left frontalis muscle as well as in the left orbicularis oculi muscle (60% increased jitter, 20% blockings; mean MCD of 125 μs; Fig. 2). EMG revealed abnormal spontaneous activity [fibrillations, positive sharp waves (psw); Fig. 1c] in the frontalis, orbicularis oculi and splenius capitis muscles and polyphasic motor unit potentials (MUPs), indicating ongoing reinnervation. EMG in other limb and trunk muscles was normal.

Due to absent wrinkles in her forehead, the examining neurophysiologist (ARP) inquired about previous facial BoNTA injections. The patient acknowledged symptom onset a few days after a “botox party”, where she and her friends received bilateral BoNTA injections around the orbicularis oculi muscle area by a nurse. She had also received regular BoNTA injections at a beauty clinic to the orbicularis oculi and glabellar area. Since the patient’s clinical presentation was not consistent with MG nor ALS, but rather consistent with a consequence of repeated facial muscle BoNTA injections, a 2-month-follow-up examination was recommended.

Two months later, most symptoms had disappeared, except for minimal dysphagia and neck muscle weakness. Jitter was increased in the left orbicularis oculi (mean MCD of 62 μs) and the left frontalis muscle but was normal in the left deltoid muscle (mean MCD of 25 μs). EMG revealed slight spontaneous activity

![Fig. 1. 3 Hz repetitive nerve stimulations study with stimulation of the facial nerve and recording over the right nasalis muscle showing normal compound motor action potential amplitudes without decrement in A) Case 1 and B) Case 2. Concentric needle EMG showing spontaneous activity of positive sharp waves and fibrillations recorded in the left frontalis muscle on the first examination in C) Case 1 and D) Case 2).](image-url)
the BoNTA therapy for migraine. Therefore, we recommended that he discontinue BoNTA injections. Therefore, we concluded that the disturbed neuromuscular transmission of the left orbicularis oculi muscle was likely due to his numerous injections (psw) and ongoing reinnervation in the left frontalis muscle and no spontaneous activity in the left orbicularis oculi.

In conclusion, improvement of the bulbar symptoms and the neurophysiological findings supports the hypothesis that the patient's symptoms were caused by BoNTA diffusion to the nearby facial muscles following orbicularis oculi injections. She was advised to avoid further BoNTA injections and did not return for additional neurophysiological nor neurological evaluations.

2.2. Case 2

A 46-year-old male patient with episodic double vision and right-sided ptosis during two months was referred for neurophysiological evaluation of ocular MG. Serum AChR antibodies were negative. There was no obvious diurnal pattern or other symptoms of generalized/bulbar fatigue. His general and neurological physical examinations were normal, except for right-sided ptosis, and ocular status was normal. MRI of the brain and carotid vessels was normal.

RNS (3 Hz) revealed no decrement in the abductor digiti minimi, deltoid, nasalis and frontalis muscles. Again, the CMAP amplitudes were within the normal range and did not increase after 20 s of maximal voluntary contraction (Table 1). Increased jitter (38%) was seen on the voluntary CNE of 16 potential pairs in the left orbicularis muscle (mean MCD of 37 μs; Fig. 2). EMG revealed slightly abnormal spontaneous activity in the left frontalis muscle and signs of reinnervation (unstable polyphasic MUPs). From the charts of a private migraine clinic, he had received 14 treatments of 155 IU of Dysport divided between a total of 31 points (~3 IU/injection point) in his facial and head/neck muscles. He received this regular migraine treatment approximately 2 weeks before the onset of his extraocular fatigue.

Based on the neurophysiological evaluation and the clinical history, we concluded that the disturbed neuromuscular transmission in the orbicularis oculi muscle was likely due to his numerous BoNTA injections. Therefore, we recommended that he discontinue the BoNTA therapy for migraine.

At follow-up four months later, his ocular symptoms had resolved, and neurological examination was normal. CNE jitter analysis in the left orbicularis oculi and routine needle EMG of the facial muscles were also normal. In conclusion, the evidence indicated normalization of neuromuscular transmission and not ocular MG.

Table 1

| Muscle          | At rest CMAP amplitude | Decrement | After 20 s of maximal contraction CMAP amplitude | Decrement | 1 min after contraction CMAP amplitude | Decrement |
|-----------------|------------------------|-----------|-----------------------------------------------|-----------|--------------------------------------|-----------|
| Case 1          |                        |           |                                               |           |                                      |           |
| Right anconeus  | 3.4 mV                 | 0%        | 3.6 mV                                        | 3%        | 3.6 mV                               | 3%        |
| Right trapezius | 6.0                    | 4%        | 6.3                                           | 5%        | 6.3                                  | 3%        |
| Right nasalis   | 0.9                    | 2%        | 1.0                                           | 1%        | 1.0                                  | 1%        |
| Right deltoideus| 6.3                    | 2%        | 6.1                                           | 2%        | 6.1                                  | 1%        |
| Case 2          |                        |           |                                               |           |                                      |           |
| Right ADM       | 12.2                   | 0%        | 13.4                                          | 2.5%      | NA                                   | NA        |
| Right deltoideus| 11.9                   | 0%        | 11.9                                          | –1%       | 11.2                                 | 5.1%      |

Fig. 2. Concentric needle EMG jitter analysis during voluntary contraction for Case 1 (A) and Case 2 (B) in the left orbicularis muscle illustrating increased jitter.

3. Discussion

Aesthetic BoNTA injections into facial muscles are more likely to be administered by non-physicians, and although generally considered safe, the spread of BoNTA into neighboring muscles especially in the face is considerable (Alimohammadi et al., 2014; Cote et al., 2005; Cavallini et al., 2014; Ramirez-Castaneda et al., 2013). In the literature, reports exist of suspected MG in association with cosmetic BoNTA use (Alaraj et al., 2013; Farooq et al., 2009; Parikh and Lavin, 2011; Sunness and Kelman, 2004). All these cases presented with ptosis, and one case with additional diplopia, which naturally raised the suspicion of MG. In one of our patients the symptoms extended from ptosis and diplopia to dysarthria and neck muscle weakness, raising suspicion of bulbar ALS in addition to MG from the referring neurologist. In contrast to the previously reported cases that lack objective neurophysiological evaluation to prove impaired neuromuscular transmission, the distinguishing feature in our cases was normal RNS and quite remarkably increased jitter and signs of denervation and reinnervation in muscles surrounding the injection sites. This is in line with previous reports on BoNTA spread from one side of the face to the other, objectively verified with EMG and SFEMG (Punga et al., 2015). The typical finding of post-exercise CMAP increment considered highly specific for human botulism caused by Clostridium botulinum bacteria is rarely seen in patients with iatrogenic botulism, although the available data on neurophysiological abnormality pattern in this condition are limited. A recent report reported absence of decremental and incremental response on RNS although SFEMG demonstrated abnormal jitter with blocks with slightly reduced CMAP amplitudes (Leonardi et al., 2019). We also noted in our two cases that patients were unable to maintain steady voluntary contraction during SFEMG recordings for sustained time.

Intriguingly, patients do not automatically inform their physicians about cosmetic BoNTA use, which is instead often reported...
“en-passant” or by direct questioning by the examining neurophysiologist. Further, patients may not be aware of the possible risks of BoNTA therapy and do not connect BoNTA exposure to the development of muscle weakness/fatigue. Additionally, BoNTA exposure may not be reported in referrals to a neuromuscular specialist by neurologists and other physicians. These cases highlight the importance of inquiring about previous BoNTA injections prior to considering sometimes uncomfortable, invasive, and costly electrophysiological investigations to exclude MG in patients who present with facial muscle weakness. Also, it is essential that patients be informed about possible side effects and complications of BoNTA therapy prior to injection. These interventions may reduce the risk of incorrect diagnoses of neuromuscular transmission disorders in patients actually experiencing an adverse effect from BoNTA injections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Alaraj, A.M., Oystrekk, D.T., Bosley, T.M., 2013. Variable ptosis after botulinum toxin type a injection with positive ice test mimicking ocular myasthenia gravis. J. Neuroophthalmol. 33 (2), 169–171.

Alimohammadi, M., Andersson, M., Punga, A.R., 2014. Correlation of botulinum toxin dose with neurophysiological parameters of efficacy and safety in the glabellar muscles: a double-blind, placebo-controlled, randomized study. Acta Derm. Venereol. 94 (1), 32–37.

Cavallini, M., Cirillo, P., Fundaro, S.P., Quartucci, S., Sciuto, C., Sito, G., Tonini, D., Trocchi, G., Signorini, M., 2014. Safety of botulinum toxin A in aesthetic treatments: a systematic review of clinical studies. Dermatol. Surg. 40 (5), 525–536.

Cote, T.R., Mohan, A.K., Polder, J.A., Walton, M.K., Braun, M.M., 2005. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. J. Am. Acad. Dermatol. 53 (3), 407–415.

Farooq, S., Dukht, U., Jaffar, S., 2009. Unilateral ptosis: a rare presentation. J. Pak. Med. Assoc. 59 (5), 319–321.

Girlanda, P., Quartarone, A., Sinicropi, S., Nicolosi, C., Messina, C., 1996. Unilateral injection of botulinum toxin in blepharospasm: single fiber electromyography and blink reflex study. Mov. Disord. 11 (1), 27–31.

Leonardi, L., Haggiag, S., Petrucci, A., Lispi, L., 2019. Electrophysiological abnormalities in iatrogenic botulism: two case reports and review of the literature. J. Clin. Neurosci. 60, 138–141.

Parikh, R., Lavin, P.J., 2011. Cosmetic botulinum toxin type A induced ptosis presenting as myasthenia. Ophthalmic Plast. Reconstr. Surg. 27 (6), 470.

Punga, A.R., Eriksson, A., Alimohammadi, M., 2015. Regional diffusion of botulinum toxin in facial muscles: a randomised double-blind study and a consideration for clinical studies with split-face design. Acta Derm. Venereol. 95 (8), 948–951.

Ramirez-Castaneda, J., Jankovic, J., Comella, C., Dashitipour, K., Fernandez, H.H., Mari, Z., 2013. Diffusion, spread, and migration of botulinum toxin. Mov. Disord. 28 (11), 1775–1783.

Sunness, J.S., Kelman, S., 2004. Cosmetic botox injection mimicking myasthenia gravis. Plast. Reconstr. Surg. 113 (5), 1515.

Table 2
Overview of reported cases of botulinum toxin application resulting in a clinical picture mimicking MG. BoNTA, botulinum toxin A.

| Age | Gender | Clinical presentation | Cause of BoNTA injections | Diagnosis of MG | Year of report | Reference |
|-----|--------|-----------------------|---------------------------|-----------------|----------------|-----------|
| 70  | Female | Diplopia, ptosis      | Cosmetic                  | –               | 2004          | Sunness and Kelman, 2004 |
| 41  | Female | Unilateral ptosis     | Cosmetic                  | –               | 2009          | Farooq et al., 2009 |
| 58  | Female | Unilateral ptosis     | “botox party”             | –               | 2011          | Parikh and Lavin, 2011 |
| 52  | Female | Unilateral ptosis     | Cosmetic                  | –               | 2013          | Alaraj et al., 2013 |
| 56  | Female | Dysphagia, neck weakness, unilateral ptosis | Cosmetic, “botox party” | – | 2020 | Current study |
| 47  | Male   | Diplopia, ptosis      | Migraine treatment        | –               | 2020          | Current study |