

Case Report

Cosmetic Injection of Botulinum Toxin Unmasking Subclinical Myasthenia Gravis: A Case Report and Literature Review

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Keywords

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Abstract

Cosmetic or therapeutic use of botulinum toxin type A (BoNT-A) is usually safe but can rarely cause iatrogenic botulism. Iatrogenic botulism and myasthenia gravis (MG) share similar clinical features, because both BoNT-A and anti-acetylcholine receptor antibodies impair neuromuscular transmission. We report a patient who underwent cosmetic BoNT-A injection and later developed serious local and systemic adverse reactions. The peculiarity of this case is that a latent seropositive MG was eventually discovered, suggesting that both iatrogenic botulism and MG contributed to the clinical picture. This patient is one of the less than 10 reported cases worldwide in whom MG was unmasked by BoNT-A injection. He is the first to be assessed in detail by single-fiber electromyography. This case emphasizes the risk associated with BoNT-A injection in patients with subclinical impairment of neuromuscular transmission and prompts the search for MG in case of exaggerated response.

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Introduction

Local injection of botulinum toxin type A (BoNT-A) is frequently conducted for therapeutic or cosmetic purposes, and is most often safe. Possible complications are mainly related to local or systemic toxin diffusion. BoNT-A *local* spread to adjacent muscles is common and is generally transient. For instance, dysphagia is not rare after toxin injection for cervical dystonia, as well as eyelid ptosis after periocular injection. BoNT-A *systemic* diffusion can also occur but generally with no clinical consequences. Indeed, single-fiber electromyography studies have shown altered neuromuscular transmission in muscles distant from the injection site without any associated symptom [1, 2]. Nevertheless, in rare cases, systemic diffusion leads to clinical manifestations of variable severity (dysphagia, generalized muscular weakness, respiratory failure, ...) [3–5]. This condition, referred to as iatrogenic botulism, remains exceptional in healthy subjects and often results, at least in cosmetic cases, from inappropriate injections of unlicensed toxins in beauty salons [6]. By contrast, in patients with an underlying neuromuscular disease such as myasthenia gravis (MG), the potency of BoNT-A is increased, even at low dose. This increased sensitivity can be explained by synergistic effects of BoNT-A and MG on neuromuscular blockade. Here, we highlight this phenomenon by reporting a patient in whom BoNT-A administration unmasked subclinical MG.

Case Report

A 43-year-old man with unremarkable medical history and no chronic medication was admitted to the emergency department for bilateral eyelid ptosis and binocular diplopia gradually worsening for 10 days (Fig. 1). Symptoms were initially mild but progressed in a few days to nearly complete eyelid closure and external ophthalmoplegia. Six weeks before symptom onset, the patient had received cosmetic injection of abobotulinum toxin A (Azzalure®; Galderma) to the glabellar, forehead, and lateral canthal rhytids (total of 84 U in one session). A similar injection had been performed 2 years earlier with no adverse effect. Neurological examination was entirely normal apart from ocular signs. Conventional blood tests, cerebrospinal fluid analysis, and brain magnetic resonance imaging were normal. A first electroneuromyography (ENMG) showed normal parameters: normal nerve conduction velocities and latencies (fibular and sural nerves), normal amplitudes of the compound muscle action potential (CMAP), decremental responses <10% during repetitive nerve stimulation (RNS) at 3 Hz of the facial nerves (nasalis, orbicularis oculi), right ulnar nerve (abductor digiti minimi), and radial nerve (anconeus). However, a single-fiber study (SFEMG) of the left orbicularis oculi showed major impairment of neuromuscular transmission (mean jitter of 112 µs with 50% blocking). Interestingly, in most neuromuscular junctions, jitter and blocking were greater with low discharge rates (5 Hz) than with high ones (40 Hz), suggesting a presynaptic disorder (Fig. 2). Based on these clinical and electrophysiological data, a local effect of BoNT-A was suspected. The patient was first treated with oral pyridostigmine 240 mg/day, based on the intuition that it would help neuromuscular transmission, but to no avail. By contrast, subcutaneous neostigmine 0.25 mg every 2 h was associated with a rapid but moderate clinical improvement. This treatment was nonetheless discontinued after a few days due to significant bradycardia. Two weeks later, the patient experienced further clinical deterioration with

worsening of the eyelid ptosis, dysphagia, and subjective generalized weakness. Repetitive nerve stimulation at 3 Hz revealed, this time, decremental responses in all muscles tested (decrement in percentages of area: right nasalis 35%, left nasalis 36%, right trapezius 26%, right anconeus 24%, right abductor digiti minimi 29%). Repair of decremental response was recorded in the right abductor digiti minimi (6 vs. 29%) after 1 min of voluntary contraction, followed by a worsening of decremental response (37 vs. 29%) 3 min after this effort, suggesting a postsynaptic disorder. Serum acetylcholine receptor antibodies (anti-AChR) were measured in the hypothesis of MG and went back strongly positive at 6.4 nmol/L (normal values <0.5), which was confirmed by a second test. Therefore, the simultaneous diagnosis of MG was established. Computed tomography of the chest showed no thymoma. Pyridostigmine treatment was gradually resumed (without significant bradycardia) in combination with oral methylprednisolone 1 mg/kg. Slowly progressive clinical improvement was then observed; dysphagia and generalized weakness completely resolved in 4 weeks, while moderate ptosis and ophthalmoparesis persisted for more than 6 months.

Discussion

To our knowledge, this patient is the 8th case reported in the literature of latent MG, revealed by BoNT-A injection [7–14], and the most documented case from an electrophysiological point of view. These different cases are listed in Table 1. It should be noted that 7 other cases of BoNT-A injection have been reported in patients with already diagnosed myasthenia [15–21].

BoNT-A inhibits *presynaptic* release of acetylcholine at the neuromuscular junction, whereas MG antibodies block acetylcholine receptors on the *postsynaptic* side. The combination of the two mechanisms has therefore synergistic detrimental effect on neuromuscular transmission. This phenomenon probably explains the clinical manifestations observed in our patient. In this case, the purely ocular and steady (i.e., nonfluctuating) nature of the initial symptoms as well as the history of recent periocular BoNT-A injection strongly suggested a local action of BoNT-A. However, the subsequent occurrence of clinical deterioration associated with dysphagia and generalized weakness could not be explained by the local effect of the toxin alone and suggested the existence of a systemic process related to the toxin itself (iatrogenic botulism) or to a neuromuscular disorder, or both. The presence of AChR antibodies, the partial response to neostigmine, and the highly suggestive electrophysiological picture eventually led to the diagnosis of MG. We surmise that MG was latent, and that BoNT-A injection brought it to the symptomatic threshold by its usually subclinical action on neuromuscular junction in both local and remote muscles. In other words, neuromuscular transmission, already jeopardized on its postsynaptic side by subclinical effects of anti-AChR antibodies, eventually failed when the toxin disturbed its presynaptic component.

Our patient experienced an unusually long delay between BoNT-A injection and symptom onset (about 6 weeks). This contrasts with the other reported cases whose latency period ranged from 1 to 36 days [6]. We do not know the reason for this delayed course. Another interesting aspect is the history of a previous injection session, 2 years earlier, without adverse event. This feature is actually observed in other cases of iatrogenic botulism (with or without MG), where complications only occur after several injection sessions [5, 8, 13, 22].

One possible explanation might be that toxin spread is highly unpredictable and varies substantially from one injection to another. Finally, it should be stressed that our patient suffered from significant complications despite the use of usual BoNT-A doses. Similar findings have been observed in previously reported cases, with doses as low as 12 U sufficient to trigger symptoms [15]. This highlights the increased sensitivity of patients with neuromuscular disease to the effects of BoNT-A. It should be noted, however, that other patients with MG have been successfully treated with BoNT-A without complications [16, 17, 19].

Electrophysiological assessment is of particular interest in this case because it combines signs of pre- and postsynaptic involvement. The expected electrophysiologic findings in human botulism are a reduction of CMAP amplitude, an incremental response of CMAP to high-rate RNS or voluntary contraction (postactivation facilitation), a moderate and inconstant decremental response to slow-rate RNS, the absence of postactivation exhaustion, and a “myogenic” pattern on needle-EMG [23–25]. It is worthy of note that these data come mainly from studies of foodborne and infant botulism rather than iatrogenic botulism. In MG, the classical electrical features are a decremental response of CMAP to slow-rate RNS, a repair of the decrement immediately after 1 min of voluntary exercise followed by a worsening of the decrement 3–4 min post exercise (postactivation exhaustion) [26]. Single-fiber EMG is virtually always abnormal in both botulism and MG (increased jitter with frequent impulse blocking) and is therefore not a discriminating test unless the discharge rate is modified [27] (see below). In this patient, the typical features of MG were found with RNS, but not those of botulism. Indeed, neither reduced CMAP amplitude nor increment have been observed (the latter may arise from the former). This does not rule out, however, the existence of botulism, since conventional EMG can remain normal in mild cases of botulism, especially in iatrogenic ones [5, 22, 28, 29]. In our patient, electrical evidence of a partly presynaptic involvement was provided only by SFEMG: jitter decreased with higher discharge rates, which is equivalent to postactivation facilitation during high-rate RNS. This effect of firing rate is suggestive of a presynaptic blockade and is usually not seen in isolated MG, where, on the contrary, jitter decreases with *slower* discharge rates [23–25, 27, 30]. Overall, the electrophysiological abnormalities encountered in our patient combined features of pre- and postsynaptic dysfunction of neuromuscular transmission.

Conclusion

The synergistic effects of MG and BoNT-A explain why patients with an underlying neuromuscular disease have an increased risk of adverse reaction after BoNT-A injection. In patients with known neuromuscular disease or obvious clinical signs (e.g., dysphagia), caution is advised and BoNT-A should be either avoided or used sparingly if there is no therapeutic alternative. By contrast, there is no practical way to identify patients with latent, subclinical neuromuscular junction abnormalities before BoNT-A administration. Indeed, screening for neuromuscular disorder through anti-AChR antibodies or EMG testing is not conceivable. Thus, a complete patient history and physical examination must be conducted before BoNT-A injection, seeking any clinical data suggestive of latent MG. If the patient presents an exaggerated response to BoNT-A, especially if he responds to acetylcholinesterase inhibitors, MG

should be considered before any further injection. Finally, an uncomplicated prior injection does not guarantee the absence of side effects after subsequent injections, even at low doses.

Statement of Ethics

The authors have no ethical conflicts to disclose. Informed consent for patient information and images to be published was provided by the patient.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Each author contributed to the treatment of the patient and diagnosis of the disease.

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Fig. 1. A 43-year-old man presenting with constant bilateral eyelid ptosis and external ophthalmoplegia gradually worsening for 10 days.

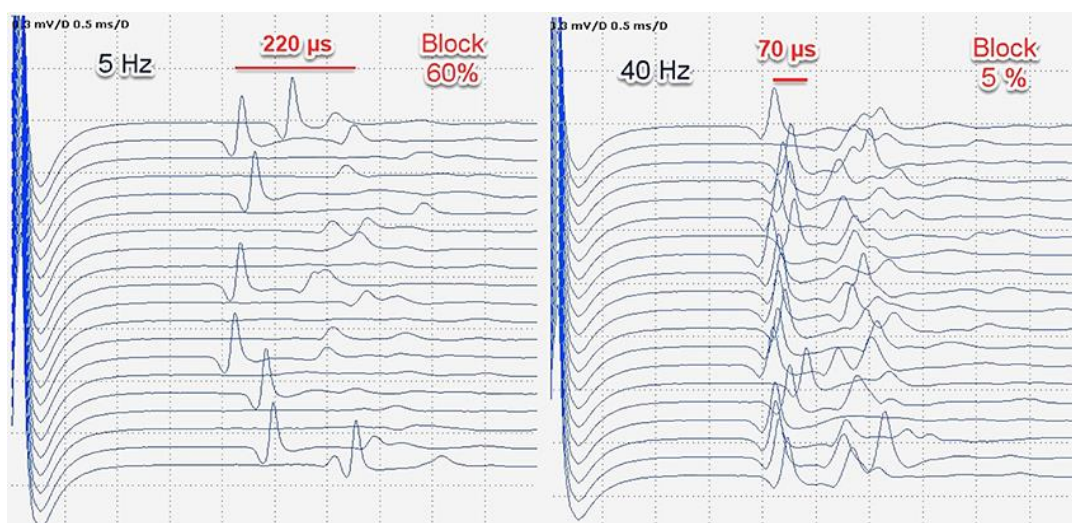


Fig. 2. SFEMG results of the left orbicularis oculi showing increased jitter with impulse blocking. In most neuromuscular junctions, mean jitter value and percentages of blocking decreases as the firing rate increases, which suggests presynaptic abnormalities.

Table 1. Comparison of patients with latent (unknown) MG unmasked by BoNT-A injection

First author, year [Ref. No.]	Indication (age, sex)	Muscles injected	BoNT-A dose (type)	Prior BoNT-A injections	Symptoms (latency/duration)	ENMG findings
Brunnschweiler, 1997 [7]	Therapeutic: cervical dystonia (56, F)	Splenius capitis	12.5 ng (Dysport)	Unspecified	Dysphagia, chewing muscles weakness, dyspnea (3 weeks/unspecified)	Decrement (% unspecified) in left deltoid and left “facial”
Borodic, 1998 [9] then Tarsy, 2000 [8]	Therapeutic: blepharospasm, oromandibular dyskinesia (80, F)	Orbicularis oculi, lower facial	120 U (Botox)	18 injections (30–120 U) over the past 13 years with no complication	Ptosis, diplopia, dysarthria, dysphagia, generalized weakness (4 days/5 months)	Normal RNS ↑ jitter in posterior cervical and upper extremity muscles
Iwase, 2006 [10]	Therapeutic: blepharospasm (78, F)	Orbicularis oculi	40 U (unspecified)	2 injections (80 U and 60 U) 1 month and 4 months earlier, with no complication	Dysphagia, dysarthria, generalized weakness (1 week/3 months)	Unspecified
Dressler, 2010 [11]	Therapeutic: cervical dystonia (66, F)	Sternocleidomastoideus, splenius capitis, trapezius	72 U (Botox)	6 injection series (72–180 U) with unspecified timing	Diplopia (1 month/unspecified)	Unspecified (pathological serial stimulation)
Glick, 2013 [12]	Cosmetic: glabellar and lateral cantal rhytids (64, F)	Periocular	58 U (unspecified)	1 injection 8 months earlier (25 U), with no complication	Diplopia (1 week/unspecified)	Unspecified
Durmuş-Tekçe, 2016 [13]	Therapeutic: oromandibular dystonia (80, F)	Hyoglossus	10 MU (unspecified)	8 injections (10 U), every 3 months before the occurrence, with no complication	Ptosis, diplopia, dysphagia, dyspnea, generalized weakness (10 days/6 months)	RNS: dysfunction of neuromuscular junction
Chegini, 2017 [14]	Cosmetic: facial rhytids (30, F)	Unspecified	Unspecified	2 injections during the preceding months, with no complication	Ptosis, diplopia, dysphagia, dysarthria, dyspnea, generalized weakness (the preceding months/unspecified)	RNS: signs of pre- and para-synaptic myopathy
Timmermans (this report)	Cosmetic: glabellar and lateral cantal rhytids (43, M)	Periocular	84 U (Azzalure)	1 injection 2 years earlier, with no complication	Ptosis, diplopia, dysphagia, generalized weakness (6 weeks/>6 months)	↑ jitter (orbicularis oculi), decrement