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Technical note

Electrophysiological abnormalities of the neuromuscular transmission in two patients with botulism-like syndrome following Botulinum-A muscle injections

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ABSTRACT

Botulinum neurotoxin serotype A (BoNT-A) has several therapeutic indications such as spasticity and dystonia. Although its use is generally considered safe, a systemic diffusion can lead to systemic complications, and a botulism-like syndrome can occur after intramuscular injections. Herein, two adult cases who developed general muscle weakness after a BoNT-A intramuscular injection are reported. Both presented with a progressive decrement on low-frequency (LF) repetitive nerve stimulation (RNS). It is suggested that a progressive decrement on LF-RNS in muscles distant from the injection site strongly supports the diagnosis of iatrogenic botulism.

Introduction

Botulism, a potentially fatal acute flaccid paralysis associated with oculobulbar symptoms and dysautonomia, is caused by the botulinum neurotoxin produced by *Clostridium botulinum* [13]. This toxin blocks neuromuscular and autonomic transmission at the presynaptic level through different proteins of the SNARE complex (SNAP-25, VAMP, or syntaxin), which are required for the fusion of acetylcholine (ACh)-containing vesicles with the presynaptic membrane [13]. Botulinum neurotoxin serotype A (BoNT-A) locally injected has several therapeutic indications, such as strabismus, blepharospasm, cervical dystonia, primary axillary hyperhidrosis, migraine, and spasticity [1]. Although the use of BoNT-A is usually considered to be safe, local or systemic side effects can occur, such as nausea, rash, fatigue, and flu-like symptoms [11]. In the literature, a clinical phenotype mimicking botulism has been reported in several patients [2,3,5,7,10,16–19]. This condition, called iatrogenic botulism (IB) or "pseudo-botulism", is thought to be caused by systemic spreading of the locally injected toxin. An electrodiagnostic (EDX) evaluation, composed of repetitive nerve stimulation (RNS) and search for a post-effort increment, is an important tool to make the diagnosis of neuromuscular junction (NMJ) disorders, including botulism and IB. However, electrophysiological data on patients with IB are scarce, particularly regarding exploration of the NMJ. Herein are reported two cases of adult patients presenting with a botulism-like syndrome following intramuscular injections of BoNT-A, in whom electrophysiological findings support a defect in neuromuscular transmission. Informed consent was obtained from patients included in the study.

Cases (Table 1)

Patient 1

The first case was a male patient with a history of ischemic stroke at 73 years old, causing a left spastic hemiparesis. A year after the stroke, due to a hammer toe, he received three intramuscular injections of 50 U BoNT-A (incobotulinumtoxinA, Xeomin®) in the left flexor hallucis longus, which were well tolerated. At 76 years, he was administered a fourth injection of 800 U (abobotulinumtoxinA, Dysport®) in the left flexor hallucis longus, gastrocnemius, and soleus muscles. One week after this last injection, he developed a generalized fatigability associated with walking difficulties and dyspnea. Apart from left spasticity, his clinical examination was unremarkable, without focal muscle weakness, nor defect in accommodation. He did not complain of visual disturbance or dysphagia. The EDX study performed one month after the injection found low compound muscle action potentials (CMAP) in right and left tibial, and in fibular nerves, as well as low sensory nerve action potential (SNAP) amplitudes in the lower limbs (right sural and right superficial

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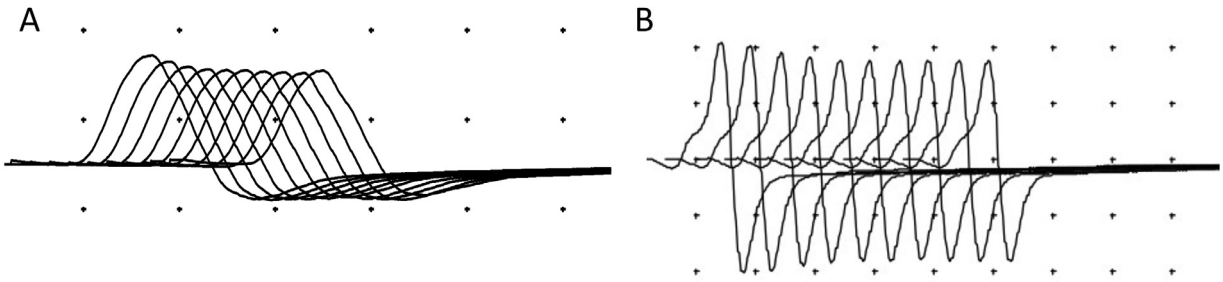

Fig. 1. Decrement after low-frequency repetitive nerve stimulation. **A**: Patient 1: Early decrement: −11.1 % decrement between the 1st and 4th responses on abductor pollicis brevis (median nerve); Late decrement: −14.9 % between the 1st and 9th responses. Late/Early = 134 %. (5 mV/div, 5msec/div). **B**: Patient 2: Early decrement: −13 % between the 1st and 4th responses on anconeus (radial nerve); Late decrement: −17 % between the 1st and 9th responses. Late/Early = 131 % (1 mV/div, 50msec/div). Both decrements had a progressive pattern, without U-shape. .mV: millivolt, msec: millisecond, div: division.

fibular nerves), probably due to a toxic polyneuropathy (previous Vincristine treatment for a follicular lymphoma). There was an amplitude decrement of at least 10 % in several muscles found on low frequency (3 Hz)-repetitive nerve stimulation (LF-RNS, right ulnar to abductor digiti minimi, median to abductor pollicis brevis, radial to anconeus, and fibular to tibialis anterior) with a maximal value of −14 %; all decrements presented a progressive pattern (Fig. 1A; Supplementary Table 1). A post-exercise CMAP increment (tested in eight muscles) was not observed, especially in muscles with low CMAP. High-frequency (30 Hz)-RNS was not performed. Needle examination at rest revealed myokymia in the right tibialis anterior muscle and fibrillations in the right medial gastrocnemius, which were the only muscles tested. During contraction, motor unit action potentials (MUAPs) were polyphasic, with a high amplitude, and the recruitment was reduced. Acetylcholine receptor (AChR) and anti-muscle-specific tyrosine kinase (MuSK) antibodies were negative. Four months after the injection, he reported a resolution of fatigability, and his walking distance returned to its basal level. The RNS was repeated 10 months after the causal injection and found no pathologic amplitude decrement. Needle EMG was not repeated. No further BoNT-A injection was performed.

Patient 2

The second case was a 29-year-old female patient who presented with spasticity of the left hemibody secondary to a hemorrhagic brain metastasis of ovarian choriocarcinoma; she received BoNT-A intramuscular injections in several muscles of the left upper and lower limbs. Injections were performed every 6 months and by the age of 35 years, the patient had received a total cumulative dose of 100 U of Botox® (onabotulinumtoxinA) and 5300 U of Dysport® (Table 1). Two weeks after her last dose of 1100 U (Dysport®), she developed fatigability and the clinical examination revealed a proximal muscle weakness on her right upper and lower limbs (4/5 on the modified Medical Research Council scale). No visual disturbance or dysphagia were noted. The EDX study performed one month after the injection found normal CMAP, without post-exercise increment. However, there was an amplitude decrement of at least 10 % in several muscles found on LF-RNS (right radial to anconeus, axillary to deltoid, and fibular to tibialis anterior), with a maximal value of −24 % of amplitude, with a progressive pattern (Fig. 1B, Supplementary Table 1). No facilitation on HF-RNS was found in muscles distant from the injection site (only a 98 % facilitation in left tibial to lateral gastrocnemius, a previously injected muscle). Needle examination at rest was normal, and during contraction, MUAPs were polyphasic and recruitment was reduced. AChR and anti-voltage gated calcium channel (VGCC) antibodies were negative. Four months after the causal BoNT-A injection, the patient did not complain of fatigability anymore and her neurological examination returned to its basal state. The RNS at this time did not find any decrement on RNS. Needle EMG was not repeated. No further BoNT-A injection was performed.

Table 1
Clinical and electrophysiological characteristics of the two patients.

	Patient 1	Patient 2
Sex and Age, years	Male, 76	Female, 34
Muscles injected	Left flexor hallucis longus, gastrocnemius, soleus, and tibialis posterior muscles	Left biceps brachii, brachialis anticus, brachioradialis, flexor digitorum sublimis, opponens pollicis, gastrocnemius, soleus, and tibialis posterior muscles, flexor digitorum longus, flexor hallucis longus muscles
Total BoNT-A dose, U, Type	150 U Xeomin®, 800 U, Dysport®	100 U Botox®, 5300 U, Dysport®
Last BoNT-A dose, U, Type	800 U, Dysport®	1100 U, Dysport®
Indication for BoNT-A injection	Spasticity (Ischemic stroke)	Spasticity (Brain metastasis of ovarian choriocarcinoma)
Symptoms after causal BoNT-A injection	Fatigability, walking difficulty, dyspnea	Fatigability, proximal muscle weakness
Time between causal BoNT-A injection and symptoms onset, weeks	1	2
CMAPs	Not interpretable (Low in lower limbs, but probably due to an axonal polyneuropathy)	Normal
LF-RNS decrement between the 1st and 4th responses (maximal value)	Yes, in 4/6 muscles (−14 %), all progressive	Yes, in 3/7 muscles (−24 %), all progressive
Post-exercise increment	No in 8 muscles	No in 2 muscles
HF-RNS increment (maximal value)	Not tested	Yes, in left lateral gastrocnemius*

CMAP: compound muscle action potential, F: female, M: male, MUAP, motor unit action potential, LF, low frequency (3 Hz), HF, high frequency (30 Hz), RNS, Repetitive nerve stimulation, BoNT-A, Botulinum neurotoxin serotype A.

* 98 % facilitation but in a previously injected muscle; no facilitation on HF-RNS was found in muscles distant from the injection site.

Discussion

Herein are reported two cases of systemic botulism-like syndrome following BoNT-A intramuscular injection, called iatrogenic-botulism (IB). Published cases are rare and these two patients reinforce that electrophysiological abnormalities should lead clinicians to consider this rare condition. To our knowledge, only 11 publications, written in English, including 20 patients, provided clinical and electrophysiological data on patients with IB following therapeutic BoNT-A intramuscular/intradermal injection. However, these data are frequently incomplete since there is only available LF-RNS data in 13 patients, HF-RNS data in 4, post-exercise increment results in 8, needle electromyography findings in 16, and CMAP amplitudes at rest in 12 [2–5,7,8,10,16–19].

The two patients reported herein presented with a decrement on LF-RNS, which strongly supports a defect of the neuromuscular transmission. As in non-iatrogenic botulism, a decrement is not systematically observed in IB. However, it was already found in 9/13 patients (69 %) [3,5,7,16,19]. The pattern of decrement on RNS seems to be also important in IB as described in other NMJ disorders. In the two patients herein, the pattern was progressive in all tested muscles, as in all the four previously published patients for whom an illustration of the decrement was available [7,16,17]. This progressive pattern is well described in the Lambert-Eaton myasthenic syndrome (LEMS) but is more rarely observed in myasthenia gravis (MG); it was especially found in cases of MG associated with MuSK antibodies (MuSK-MG) [12,15]. In LEMS and MuSK-MG, a presynaptic defect is well described, it is responsible for an impaired ACh release that cannot be compensated by ACh from other pools [12,15]. Conversely, in MG associated with AChR antibodies, a release of ACh from other pools after the 4–5th response is responsible for a U-shaped LF-RNS decrement, indicating an isolated post-synaptic defect [14]. Thus, in a patient who received a recent intramuscular BoNT-A injection and who presents with compatible clinical symptoms, a decrement with a progressive pattern on LF-RNS should lead clinicians to consider an IB. In all the reported cases, for whom this information was available, there was a moderate decrement (maximal value < 25 %), as found herein [3,5,16,17].

A CMAP increment on HF-RNS distant from the injection site was not found in our patients. However, it was found in 1/4 of previously reported patients with available data [7,19]. Regarding the post-exercise increment, it was not present in the two patients of the present study and was only positive in 2/8 patients already reported [7,10,16,17]. Thus, it seems to be a rare feature of IB and not a sensitive EDX abnormality.

Importantly, the presence of electrophysiological abnormalities supporting a defect in neuromuscular transmission, such as decrement or increment, could be present regardless of the BoNT-A dose [7,10]. Decrements in LF-RNS could be observed with the two types of BoNT-A (Dysport® or Botox®) [3,7,16,17]. Unfortunately, the delay between injection and EDX study was not clearly stated in the reported patients without decrement. It did not allow us to find a correlation between the delay of EDX study and the presence of a decrement. IB has been observed in patients receiving long-term treatments and high doses as well as in patients who received short-term treatments and lower doses [3,7,19].

A presynaptic defect is also responsible for low CMAP amplitudes, which were found in 6/12 of patients with IB (50 %) [7,8,10,19,20]. However, this feature can be non-specific and related to another confounding disease, as observed in patient 1 with polyneuropathy. Regarding needle examination, abnormal resting activities comprising fibrillations and positive sharp waves were observed in patient 1, and in 13/16 previously published patients (81 %) [2,3,5,7,8,10,16,17]. However, the myokymia observed in patient 1, was not previously described in the literature. We cannot exclude that this finding is secondary to the pre-existing toxic neuropathy. Results of recruitment and MUAPs using needle electromyography seem to be more heterogeneous, and were previously well discussed [10]. MUAPs can be of short amplitude and duration, with a polyphasic morphology, as observed in patient 2. The high amplitude MUAPs found in patient 1 seem to be secondary to his toxic axonal polyneuropathy.

It is of note that single-fiber EMG (SFEMG) is frequently abnormal in IB, due to prolonged jitter, but can also be pathogenic in asymptomatic patients after BoNT-A injections [14]. Thus, clinicians should use it cautiously and consider the clinical phenotype before diagnosing IB.

Also, symptoms appeared quickly within two weeks after the BoNT-A injections in the two patients herein, and in 14/19 (74 %) of the reported patients with available data [2–5,7,10,16–19]. This contrasts with the expected effect of BoNT-A that is delayed and appears more frequently between two and three weeks after the injection, depending on the dose, site, and indication.

Of note, numerous cases of IB following intragastric BoNT injections performed for weight loss were reported in 2023 [6]. EDX findings were reported for one patient. The nerve conduction study was normal and LF-RNS as well as HF-RNS did not find significant (<10 % and >100 %) decrement. Needle EMG showed denervation, early recruitment and narrow motor unit potentials with low and normal amplitudes [9].

In conclusion, a decrement on LF-RNS with a progressive pattern and a moderate value (<25 %) seems to be a strong argument to support the diagnosis of IB in a patient presenting with general weakness following BoNT-A injections. When not found, other features can be used as supportive diagnostic criteria, such as low CMAP values, post-exercise CMAP increment, abnormal spontaneous activities, or a prolonged jitter on SFEMG.

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Declaration of competing interest

The authors report no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.neucli.2024.102984.

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