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Letter to the Editor

Neuralgic amyotrophy following botulinum toxin injection☆

Botulinum toxin (BT) is a polypeptidic neurotoxin produced by *Clostridium botulinum* that is widely used in medicine [1]. The U.S. Food and Drug Administration (FDA) approved BT type A injection use for the treatment of cervical dystonia, blepharospasm, primary axillary hyperhydrosis and cosmetic use for glabellar lines, and it is also widely used to treat spasticity, siallorhea, chronic tension-type headache, and other diseases in ophthalmology, urology, gastroenterology, dermatology and orthopedics [1].

BT type A injections have a favourable safety and tolerability profile. Most reported adverse effects are benign and reversible, including injection site reactions [2], focal weakness [2] such as dysphagia, ptosis and strabismus, and subclinical effects on neuromuscular junctions of distant non-injected muscles [3]. Rare but potentially dangerous complications have also been described, including systemic botulism [4] and anaphylactic reactions [5], and cases of distant nerve injury have also been reported.

A 65 year-old right-handed woman was referred for BT injection for cervical dystonia of three years duration. BT type A (Botox A®) was injected to the left sternocleidomastoid and the right splenius capitis muscle (total dose of 150 units). While the patient noted improvement in neck stiffness and positioning, on the 8th day following injection, she developed excruciating left arm pain radiating from the shoulder to the elbow. The pain was severe enough to send her to the emergency room, where she was treated with oxycodone. Later that month, as the pain subsided, left arm weakness developed, including weakness of internal rotation and abduction of the arm. An MRI of the shoulder demonstrated edema of the supraspinatus and infraspinatus muscles consistent with denervation of the suprascapular nerve, without evidence of entrapment of the suprascapular nerve (Fig. 1) [6]. Nerve conduction studies of the left arm were normal except for mild left ulnar neuropathy at the elbow. Electromyogram (EMG) of the left arm showed evidence of complete left suprascapular neuropathy with fibrillations and positive sharp waves, and no recruitable motor units seen in the supraspinatus or the infraspinatus. There were 1+ fibrillations and positive sharp waves in the pronator teres and flexor carpi radialis, which may be consistent with C6–7 radiculopathy. The rest of the EMG of the left arm, including the deltoid, biceps, triceps, extensor digitorum longus, flexor carpi ulnaris and first dorsal interosseous muscles, was normal. Over the course of the following four months her pain resolved and she regained muscle strength; however, cervical dystonia symptoms persisted. Re-treating her with BT injection was deemed ill-advised.

Our patient's acute clinical presentation is consistent with Neuralgic Amyotrophy (NA) involving the upper trunk of the brachial plexus. This pattern is the most commonly seen in idiopathic cases of NA [7]. While rare, this is not the first case of NA following BT treatment. Five other cases have been previously reported and are summarized in Table 1 [8–11]. In these cases, NA usually developed after the first exposure to BT with an average latency of 7 ± 3 days. The muscles and nerves involved were distant from the injection site and, in some cases, contralateral or even bilateral. Follow-up periods were short, and complete recovery was documented in only one patient after 7 months. Pain remitted in all cases where it was present.

NA, also known as acute brachial plexitis or Parsonage-Turner syndrome, is a rare entity affecting 2–4/100.000 persons per year [12]. Epidemiological studies [7] support an inflammatory, immune-mediated pathogenesis, as half the cases are associated with antecedent viral infections, immunization or intravenous drug exposure (streptokinase, heroin, interleukin-2, interferon-α2). Further supporting immune pathogenesis is the presence of anti-ganglioside antibodies in some patients, [13] and peripheral lymphocytes sensitized to brachial plexus antigens [14]. Recurrence is not uncommon, affecting up to 26% of patients [7]. Outcome may be unfavorable in two-thirds of patients, with persistent pain or paresis at 3 years of follow-up [7].

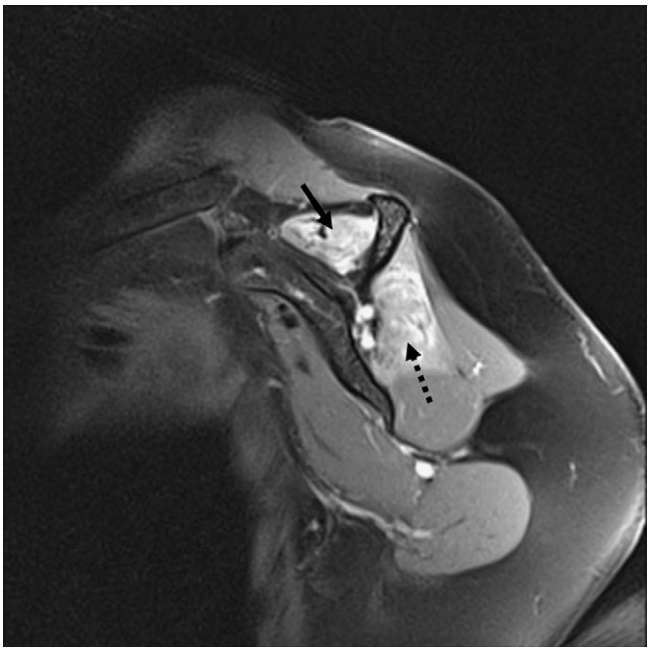

Fig. 1. Sagital proton density with fat suppression MRI of the left shoulder demonstrating hyperintense signals in the supraspinatus (black arrow) and infraspinatus (dotted arrow) consistent with acute denervation.

☆ The review of this paper was entirely handled by the Co-Editor-in-Chief, Professor R.F. Pfeiffer.

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Table 1
Summary of previous reported cases of botulinum toxin-related neuralgic amyotrophy.

Case #	Author, year	Gender	Age (yrs)	Indication for BT	BT type and formulation	First exposure	Total dose	Temporal relation	Relation to injection site	Plexus involvement	Outcome
1	Glanzman et al. [11] 1990	F	53	Cervical dystonia	A Botox®	Yes	120 U	2 days	Ipsilateral	Upper trunk	Incomplete recovery at 5 months
2	Sampaio et al. [8] 1993	F	32	Cervical dystonia	A Dysport®	Yes	1st tx: 800 U 2nd tx (+2 wks): 400 U	Pain 1 wk after 1st tx. Weakness 2 wks after 1st tx	Bilateral	Upper trunk	Not reported
3	Sheean et al. [9] 1995	F	36	Writer's cramp	A Dysport®	Yes	1st tx: 40 U 2nd tx (+7 wks): 80 U	Pain 1 wk after 1st tx. Weakness 9 wks after 1st tx. 2 wks after 2nd tx	Ipsilateral	Lower trunk	Incomplete recovery at 3 months.
4	Sheean et al. [9] 1995	F	55	Writer's cramp + laryngeal dystonia	A Dysport®	No	7th tx: 100 U 8th tx (+10 wks): 200 U	Pain 1 wk after 7th tx. Weakness 10 wks after 7th tx. 1 wk after 8th tx	Ipsilateral	Upper trunk, lower trunk, post cord	Prolonged pain (5–6 wks), recovery not reported
5	Tarsy [10]1997	M	55	Cervical dystonia	A Botox®	Yes	160 U	10 days	Contralateral	Upper trunk	Complete recovery in 7 months. Re-administration of BT without recurrence.
6	Present case	F	65	Cervical dystonia	A Botox®	Yes	150 U	8 days	Ipsilateral	Upper trunk	Complete recovery in 4 months. No re-administration of BT

BT – Botulinum toxin; wk – week.

The temporal relationship between NA and BT injection suggests a causal relationship. The injection sites were distant from the affected nerves and muscles, making direct injury of the nerves unlikely.

Cases of polyradiculopathy following botulinum toxin injections have also been reported [15–17], supporting the hypothesis of immune mediated peripheral nerve injury following BT injections. Most reported cases to date were associated with arm or neck injections; this may suggest that the site of the injection plays a role in the development of NA, or that the association between NA and BT injections elsewhere on the body (e.g. face) were missed. Given the suggested immune mediated nature of the reaction, it is possible that similar complications can arise after injection for other medical and cosmetic indications. The fact that cases have been reported with two distinct preparations of botulinum toxin type A (Botox A® and Dysport®) suggests that the antigen is the toxin itself and not another protein in the product. Whether patients who developed such a complication can be safely re-exposed to BT remains unknown, and this should, in our opinion, probably not be tested [9,15].

Disclosure
The authors report no conflicts of interest.

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