Delayed and prolonged arm weakness and atrophy following botulinum toxin injection for musician's cramp

Barbara Karp MD\textsuperscript{1}; Katharine Alter MD\textsuperscript{2}; Mark Hallett MD\textsuperscript{1}

\textsuperscript{1}Intramural Research Program, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda Maryland; \textsuperscript{2}Rehabilitation Medicine Department, Intramural Research Program, Clinical Center, National Institutes of Health, Bethesda Maryland;

Introduction

Almost 30 years' experience has established an excellent safety profile for botulinum toxin (BoNT) as the first line treatment of focal hand dystonia (FHD). Therapeutic response to BoNT for FHD is almost always accompanied by weakness in injected and nearby muscles. Weakness usually precedes clinical benefit, reaches a maximum more quickly and is of shorter duration. Weakness is directly attributable to blockade of acetylcholine release at the neuromuscular junction.

Although not always clinically apparent, even a single injection of BoNT at therapeutic doses can cause atrophy visible on ultrasound and MRI. Clinically-apparent atrophy is more likely after repeated injections into the same muscles. BoNT-related atrophy is reversible if injections are stopped.

There have been rare reports of delayed weakness and atrophy with BoNT. We report here a patient with musician's cramp, being treated with BoNT for 10 years, who developed an unusual delayed onset of severe, focal arm weakness and atrophy after the most recent injection.

Figure 1: Dystonia pattern

Figure 2: Patient's typical onset and duration of weakness

Figure 3: Ulnar forearm atrophy

3 months post-injection

14 months post-injection

Discussion

Our patient had an unusual course of severe atrophy and delayed and prolonged weakness following BoNT for FHD. Weakness was present in injected and adjacent muscles, but also in ADQ, a distal, uninjected muscle. Unlike his typical weakness which lasted a mean of 11 days after injection, this episode of weakness and atrophy lasted over a year in the absence of further BoNT injection.

Animal and clinical studies have shown that even a single BoNT injection at therapeutic doses can cause atrophy persisting for months, although such atrophy is often not clinically apparent. Muscle mass recovers gradually.

Delayed-onset, severe, prolonged weakness and atrophy have not been reported in large-scale clinical trials of BoNT. However, the literature contains rare case reports [Table]. The affected patients included both men and women being injected for a variety of indications and with onabotNTa or aboBONTA. Some patients developed this complication with their first injection; in some patients, the weakness followed a "booster" injection. Others (like our patient) had been treated over years. In a number of reported cases, the weakness and atrophy affected muscles distant from those injected and the patients had prominent pain before the onset of weakness. Such cases were associated with NCV/EMG evidence of polyneuropathy, polyradiculoneuropathy or neuromuscular amyotrophy, attributed by the treating clinicians to a possible immune-mediated process. One patient with brachial plexopathy went on to have further BoNT injection without recurrence.

In contrast, our patient had painless weakness and atrophy limited to the injected limb, including involvement of some muscles distal to the injection. Our case is thus more similar those of Glass and Zhao, with the weakness and atrophy likely a direct effect of toxin. Without further toxin injection, strength and muscle bulk recovery may be contra-indicated as it is not known if BoNT can be safely resumed after recovery.

Case report

A 66 year old RH pianist first noted his 4th and 5th fingers "hanging down" when playing scales and fast passages in 2002, at age 51. Cotsisms injections, anti-inflammatory medications, TENS and acupuncture provided no relief. In 2004, he diagnosed himself with FHD.

When first seen at NIH in 2006, physical exam was normal except for action-induced hyperflexion at the FIP joints of the right digit (D) iv and Dv when playing piano [Figure 1]. Botulinum toxin injections started at a dose of 10 Units onabotulinumtoxinA divided into FDS iv and v. Injections continued over the next 10 years at approximately 3-6 month intervals, with the dose gradually increasing. Injection of FDP (iv, v) were added in 2010. He had relatively stable benefit and mild-to moderate tolerable, temporary weakness. His weakness was typically first noticed about 1 week after injection and lasted a mean of 11± 3 days. [Figure 2]

In January 2017, he received his usual dose of 55 U onabotNTA divided into FDS iv - 15 Units, FDS v - 15 Units, FDP iv - 15 Units under ultrasound guidance. One month later, he had his usual slight (4/5) weakness limited to the injected finger flexors.

Eight weeks after injection, he reported that he had developed marked forearm weakness over the prior 2-3 weeks that was continuing to worsen. He also noticed marked atrophy of his medial forearm. He had no pain, sensory loss or systemic complaints.

He was unable to return for evaluation until 7 weeks later (3 months after injection). Examination revealed marked atrophy of the ulnar forearm [Figure 3a], with lesser atrophy of the hypothenar eminence. FDS and FDP were weaker than on prior examination. Weakness was also present in non-injected muscles—pronator teres, wrist flexors and abductor digiti quinti (ADQ) on the injected side. There was no proximal arm weakness. Biceps, brachioradialis and triceps reflexes were present and symmetric. Blood tests including ESR, CRP, and CK were normal. Nerve conduction studies and electromyography showed no evidence of ulnar nerve compression neuropathy, radiculopathy or brachial plexus lesion. Active denervation was identified in the injected muscles and un.injected muscles, including pronator teres, flexor carpi ulnaris, and ADQ.

By 7 months after injection, atrophy and weakness were resolving. He was able to play piano for about 1 hour/day. EMG showed a denervation-reinnervation pattern in the same muscles as previously.

Muscle strength was almost normal 11 months after injection with only slight residual weakness of finger flexion and his dystonia had fully returned. Muscle bulk also showed marked improvement, although residual atrophy was still apparent [Figure 3b].

When last seen 14 months after injection, he had only minimal weakness of D iv finger flexion. The EMG was improving as well.

Table: cases in the literature

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Initial</th>
<th>Drug</th>
<th>Muscle</th>
<th>Visceral</th>
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<tbody>
<tr>
<td>Patient 1</td>
<td>2010</td>
<td>15 U</td>
<td>3 days</td>
<td>1 month</td>
<td>yes</td>
<td>onabotNTA</td>
<td>FDS, FDP</td>
<td>mild</td>
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<td>Patient 3</td>
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<td>55 U</td>
<td>1 week</td>
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<td>FDS, FDP</td>
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<td>Patient 5</td>
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<td>mild</td>
</tr>
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References


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