LETTER TO THE EDITOR

To The Editor

Botulism-like Syndrome Following Botulinum-A Injection for Hyperhidrosis and Fluoroquinolone Use

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Botulism was first described in victims of food poisoning who developed a rapidly progressive descending paralysis, and has since been developed into a therapeutic agent.[1] The mechanism of action stems from an anaerobic bacterium, *Clostridium botulinum,* that secretes various serotypes of botulinum neurotoxin.[1] Botulinum Toxin A (BoNT-A) has many clinical indications including movement disorders, spasticity, migraines, pain syndromes, hyperhidrosis, and cosmetics.[1] BoNT-A is considered to be generally safe with reported side effects including injection site focal weakness, cough, fever, malaise, headache, and injection site reactions.[1] A review of the literature reveals rare reports of generalized weakness and iatrogenic botulism following therapeutic use of BoNT-A for dystonia,[2,3] hyperhidrosis,[4] spasticity,[3,5] and movement disorders.[6] We present a case of probable iatrogenic botulism following administration of BoNT-A for hyperhidrosis that is uniquely confounded by recent fluoroquinolone antibiotic use (ciprofloxacin), which also has documented action on the neuromuscular junction.[7]

A 31-year-old female was referred for assessment of hand weakness after her second trial of BoNT-A intradermal injection for hyperhidrosis. Her only comorbidities were a remote lumbar spine fusion and a recently treated urinary tract infection with ciprofloxacin. She did not have any personal or family history of neuromuscular disease. She first had a Botulinum A (Onabotulinum) injection 2 months prior to presentation, where she received 50U in each axilla (total of 100U). Two weeks prior to presentation, she had a second treatment that involved 100U of Onabotulinum A into each of her palms (2:1 dilution) and 50U into each axilla (1:1 dilution). The injections were administered in a grid pattern by a physician with extensive experience and skill using BoNT-A. She noticed symptoms 5 days following her second round of injections, which included fatigue, dry mouth, blurred vision, mild headache, and bilateral hand weakness. Her initial exam was significant for mild neck flexion weakness, fatigable deltoid weakness, and bilateral hand weakness (finger extensors 4+/5, first dorsal interossei (FDI) 4/5, abductor pollicis brevis (APB) 4−/5). Her electrophysiologic studies demonstrated decreased amplitude of the right median and ulnar nerves on motor studies (Table 1). Repetitive nerve stimulation at 2Hz (right median to APB) showed maximal decrement following maximal voluntary contraction (MVC), with maximal decrement 4 min post-MVC. Her repetitive nerve stimulation at 50Hz (right median to APB) showed facilitation of 181% (Figure 1). Electromyography (EMG) demonstrated small motor (MUAPs) suggestive of myopathic units in FDI, APB, and the deltoid. These studies are suggestive of a presynaptic neuromuscular junction localization and given her medical history, iatrogenic botulism was considered. At her 3-month follow-up, her exam had improved as she now had only mild FDI and APB weakness. Her electrophysiologic studies improved as well, with only a mildly low ulnar motor amplitude, no facilitation on rapid RNS, less decrement on slow RNS, and improved appearance of myopathic units on EMG in the hand intrinsic muscles. By 9 months, her physical exam and electrophysiology were completely normal. No other adverse events were reported among other patients who used this particular batch of Onabotulinum A.

Botulism is clinically characterized by symmetric descending paralysis that is often associated with dilated pupils, dry mouth, diplopia, ptosis, dysphagia, dysarthria, and respiratory failure.[4] Our patient demonstrated symptoms consistent with this syndrome, including visual disturbances, weakness, and dry mouth. Electrophysiology in botulism classically shows a reduced compound muscle action potential (CMAP) amplitude that increases with high-frequency repetitive nerve stimulation demonstrating facilitation, and decrement at low-frequency repetitive nerve stimulation, which was seen in our case.[2] Botulinum neurotoxin binds to the SV2 receptor on the presynaptic membrane of the neuromuscular junction, and then interferes with exocytosis of acetylcholine, which results in reduced acetylcholine released into the junction and therefore reduced muscle activation.[1] Fluoroquinolone antibiotics also act on the neuromuscular junction by chelating ionized calcium, and therefore inhibiting acetylcholine release presynaptically and may also act directly on acetylcholine receptors as well.[7] To our knowledge, this combination of drugs has not been previously reported to cause neuromuscular junction issues, however, it is likely that both contributed to our patient's presentation.

The mechanism for the involvement of sites distant from the injection of BoNT-A is controversial, with main theories including hematogenous spread, retrograde axonal transport of the toxin, or an immune-mediated phenomenon.[5] Single-fiber EMG done at sites distant from the injection site have been shown to have jitter and blocking, demonstrating a presynaptic process, even in the absence of clinical weakness or abnormal routine electrophysiologic testing.[8] It seems that higher doses of BoNT-A and repeated use may be risk factors for the dissemination of BoNT-A after local injection.[2–6] It is important for clinicians to be aware of the neuromuscular complications of commonly used medications including antibiotics and botulinum toxin.

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Table 1: Motor nerve conduction studies demonstrating low amplitudes in the right median and ulnar nerves without evidence of facilitation at 10 s due to lack of strength for significant maximal contraction

Nerve and site	Latency	Amplitude	Duration	Segment	Area	Distance	Conduction velocity	Temperature (Celsius)
Median R								
Wrist	3.7 ms	1.0 mV	6.5 ms	APB – Wrist	3.4 mVms	70 mm	m/s	32.2
Elbow	7.4 ms	1.0 mV	6.6 ms	Wrist – Elbow	3.8 mVms	194 mm	52 m/s	
Post-10 s ex	4.0 ms	1.1 mV	6.2 ms	Elbow – post-10 s ex	3.6 mVms	mm	m/s	0.0
Ulnar R								
Wrist	2.4 ms	3.2 mV	5.8 ms	ADM – Wrist	7.4 mVms	70 mm	m/s	
Below Elbow	5.7 ms	3.3 mV	5.6 ms	Wrist – Below elbow	7.4 mVms	270 mm	82 m/s	
Above Elbow	7.4 ms	3.1 mV	5.7 ms	Below elbow – Above elbow	7.3 mVms	110 mm	65 m/s	
Post-10 s ex	2.8 ms	3.5 mV	4.7 ms	Above elbow – post-10 s ex	6.5 mVms	mm	m/s	0.0
Post-10 ext	2.5 ms	3.6 mV	5.0 ms	Post-10 s ex – post-10 s ext	6.6 mVms	mm	m/s	0.0
Peroneal R								
Ankle	4.5 ms	5.7 mV	6.6 ms	EDB – Ankle	21.5 mVms	90 mm	m/s	
Fib Head	10.1 ms	5.5 mV	6.7 ms	Ankle – Fib Head	20.7 mVms	278 mm	50 m/s	
Pop Fossa	11.8 ms	5.5 mV	6.8 ms	Fib Head – Pop Fossa	20.9 mVms	88 mm	52 m/s	
Post 10 s ex	4.5 ms	5.9 mV	6.4 ms	Pop Fossa – post -10 s ex	21.7 mVms	mm	m/s	0.0
Tibial R								
Ankle	4.7 ms	16.0 mV	5.9 ms	Abd. Hall Brev – Ankle	37.7 mVms	90 mm	m/s	
Pop Fossa	13.0 ms	12.5 mV	5.3 ms	Ankle – Pop Fossa	32.6 mVms	350 mm	42 m/s	

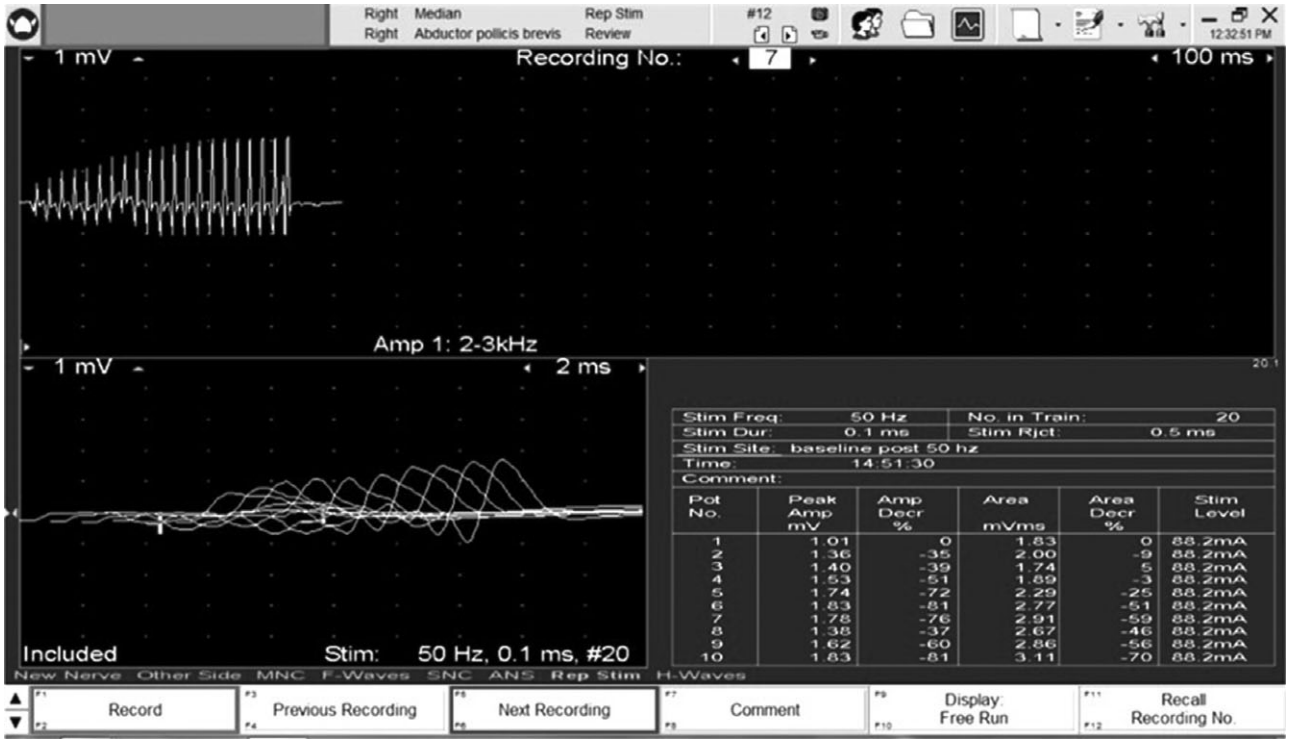

Figure 1: *50Hz repetitive stimulation waveforms demonstrating significant facilitation (181%).*

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Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

Statement of Authorship

RV was responsible for manuscript writing and literature review.

KS was responsible for project oversight, clinical guidance and discussion, and manuscript editing.

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References

1. Ney JP, Joseph KR. Neurologic uses of botulinum neurotoxin type A. Neuropsychiatr Dis Treat. 2007; 3(6): 785.
2. Bhatia KP, Münchau A, Thompson PD, et al. Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. J Neurol Neurosurg Psychiatry. 1999; 67(1): 90–3.
3. Crowner BE, Torres-Russotto D, Carter AR, et al. Systemic weakness after therapeutic injections of botulinum toxin a: a case series and review of the literature. Clin Neuropharmacol. 2010; 33(5): 243.
4. Rouientan A, Otaghvar HA, Mahmoudvand H, Tizmaghz A. Rare complication of botox injection: a case report. World J Plast Surg. 2019; 8(1): 116.
5. Bakheit AM, Ward CD, McLellan DL. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases. J Neurol Neurosurg Psychiatry. 1997; 62(2): 198.
6. Coban A, Matur Z, Hanagasi HA, et al. Iatrogenic botulism after botulinum toxin type A injections. Clin Neuropharmacol. 2010; 33(3): 158–160.
7. Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation. Drug Saf. 2011; 34(10): 839–47.
8. Lange DJ, Brin MF, Warner CL, et al. Distant effects of local injection of botulinum toxin. Muscle Nerve. 1987; 10(6): 552–5.

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