Iatrogenic generalized botulism, case report.

Mohanad Faisal[1], mohammad ghabashneh[1], Mohamed Atta[1], Liaquat Ali[1], Raza Akbar[1], and yasir osman[1]

[1]Hamad Medical Corporation

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Introduction

Botulism was first described in the literature in the 1820s after a case series including hundreds of people in a German town affected by sausage poisoning. [1] It is described as a severe neuroparalytic, life-threatening, rare disease caused by the anaerobic and spore-forming bacterium *Clostridium botulinum* . [1, 2] The exo-neurotoxin produced by the proteolytic Clostridium botulinum and non-proteolytic C. botulinum during their growth in food is potently fatal after consuming only a finite amount of around 30-100 ng. [2] There are generally around seven immunologically recognizable existing neurotoxins, identified from A to G, with types A, B, and E being the most reported. [2] Such neurotoxin, in all its existing forms, preferentially impedes neural transmission by blocking the presynaptic release of acetylcholine at the neuromuscular junction, resulting in a reversible process of muscle fiber denervation, leading to paralysis and muscle atrophy. Botulism occurs in different forms: infantile, foodborne, and wound botulism. [3] Whereas iatrogenic and adult are rare yet recognized adverse effects. [4]

Botulinum toxin A (Bix-A) has been utilized clinically in a spectrum of diseases such as spasticity, strabismus, blepharospasms, cervical dystonia, hemifacial spasms, and cosmetically. [3] Its therapeutic effect persists for nearly three months. [3] While it is generally safe and is rarely associated with significant yet life-threatening side effects, such as systemic spread of the botulinum toxin leading to systemic botulism syndrome, [4] We thereby report a patient with iatrogenic diffuse botulism post-therapeutic Botox injection for chronic back pain in a non-authorized center. This report is crucial to highlight such a rare but potentially serious side effect of this treatment and the importance of getting such treatment in authorized centers.

Case presentation

A 61-year-old female with a medical history of long-standing back pain due to multilevel degenerative spondylodiscopathies sought Botox injections in Turkey 3 weeks before admission, hoping to alleviate her chronic back pain based on information she found online. The Botox was administered bilaterally in the neck and back down to the mid-torso. The patient reported that the individual administering the injections was not a healthcare professional in a non-authorized center with no medical report about the dosage and type of Botox used.

Following the first dose of injections in late June, the patient began to feel some muscle weakness, initially affecting her eyes, voice, swallowing, and breathing, with subsequent descent to other muscle groups. She described her head as "floppy" and had difficulty getting out of bed in the morning. Additionally, she reported shortness of breath that occasionally woke her from sleep. One week before presentation, the patient received a second dose of Botox injections. The symptoms persisted and progressively worsened after this second dose. In addition to her back pain, her past medical history was significant for asthma, for which she is taking on need inhalers, and hypothyroidism, taking thyroxin. She is a nonsmoker and non-alcohol consumer. She is married with 5 kids. On presentation, her **vital signs are** temperature: 36.5°C, BP: 120/70 mmHg, and

SpO2: 98%. She was alert, conscious, and oriented; she appears fatigued but not in respiratory distress. Her chest, cardiovascular, and abdominal examinations were unremarkable.

Her neurological examination showed bilateral ptosis and bilateral facial weakness in addition to difficulty in maintaining neck position. Her **Power:** 4/5 in all limbs with hypotonia, but reflexes are preserved with down-going planters. Her sensory and cerebellar exams were unremarkable. Patient basic blood tests, including complete blood count, renal function test, and liver function tests, were unremarkable.

Methods and differential diagnosis:

Patient was admitted as case of acute flaccid paralysis, differential diagnosis was botulism based on history of botulinum toxin injections but keeping with history, age of the patient and physical examination myasthenia gravis was also considered. Descending variant of Gullian barre syndrome was also suspected but the presence of reflexes made this deferential less likely. To confirm diagnosis nerve conduction and repetitive nerve stimulation (RNS) were done and showed: Motor and sensory nerve conduction study of left median and ulnar nerves were within normal limits. Left spinal accessary and left facial nerves showed low compound muscle action potential (CMAP) amplitudes and post-exercise no CMAP amplitude increments (figure 1).

Repetitive nerve stimulation (RNS) findings: RNS and exercise testing were performed at slow 3 Hz on left ulnar, facial, and spinal accessary motor nerves (figure2). There was a significant decrement (>10%) present on the left spinal accessory motor nerve post-exercise (Figure 3). High-frequency (20 Hz) RNS on spinal accessary motor nerve showed a significant increment of 103.8% (>100%) (figure 4). The electrophysiologic findings are consistent with a presynaptic neuromuscular junction (NMJ) transmission disorder, which, in an appropriate clinical context, is suggestive of botulism. The patient managed conservatively with appropriate physical and occupational therapy in addition to speech therapy and respiratory therapy follow-up. She was discharged after two weeks to the rehabilitation institute when stability was confirmed, and signs of improvement started to appear.

Discussion:

In 1984, botulinum toxin was first reported to be successful in treating blepharospasm [5], and since then the botulinum toxin injection has been growing widely due to increased therapeutic and cosmetic application. With the growing use of the toxin, there was a significant increase in the number of iatrogenic botulisms. From May 2016 to September 2019, at least 18 cases of iatrogenic botulism have been under investigation by the Department of Health of Hong Kong. Different forms of botulinum toxin with different dosages for each site are present. [6] The effect of the botulinum toxin injection is usually local, and the incidence of generalized symptoms is extremely rare. In individuals with blepharospasm and cervical dystonia treated with Botox, only focal weakness was substantially more common (114/582, 19.6% vs. 12/383, 3.1%), according to a meta-analysis of randomized controlled trials comparing Botox (N = 1425) and placebo (N = 884).[7] Botulinum toxin A was found to be independently linked to upper lid ptosis and focal weakness on the injection side in 5/232 (2.2%) and 3/232 (1.3%) treatment sessions for hemifacial spasm.[8] A analysis of 1594 Dysport injection sessions for 758 children (94% with spastic cerebral palsy, the remaining children with various neurological illnesses) revealed 16 (1%) cases of focal muscle weakness and widespread muscle weakness in six of the children. A bad outcome was significantly predicted by a dose greater than 1000 IU. [9] The wide availability of the non-liscened centers made the botox injection subject to misuse with adverse consequences. A disease outbreak notification was released by the World Health Organization (WHO) in late March 2023, pertaining to an iatrogenic outbreak of botulism that affected 87 patients undergoing bariatric surgeries (weight loss) at two Turkish hospitals located in Istanbul and Izmir. Those impacted estimate that the current outbreak may have touched over 250 people, but authorities think there may be more victims to come. According to reports, the patients had the operations done between February 3 and March 1, 2023. The authorities have since put a stop to operations at these centers and started an internal inquiry. It has been found that intragastric botulinum neurotoxin (BoNT), an off-label usage for a popular medication in cosmetic dermatology, was administered to all affected individuals. The European Centers for Disease Prevention and Control (ECDC) have noted that the iatrogenic botulism cases linked to the current

outbreak have been reported in Germany, Austria, France, Switzerland, and Turkey [10]. Our patient admits to receiving a therapeutic botulinum toxin injection in a non-licensed center in Turkey, but she is unaware of the type and the dosage. [10]

Post-exercise or post-high-frequency repetitive nerve stimulation compound muscle action potential increment, which implies neuromuscular junction facilitation, is classically considered highly specific and sensitive in human botulism. [11] Based on the history, temporal association, and electrophysiological findings, our patient was diagnosed with botulism. patient was managed with supportive care because of the lack of availability and questionable efficacy of antitoxin in such cases.[6]

Conclusion:

The wide availability of botulinum toxin injection and increasing therapeutic and cosmetic uses make it subjected to misuse, which can lead to iatrogenic botulism, which can lead to serious consequences. Hazards of botulism toxin need to spread among health care practitioners and even publicly to decrease the potential risks.

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Glossary:

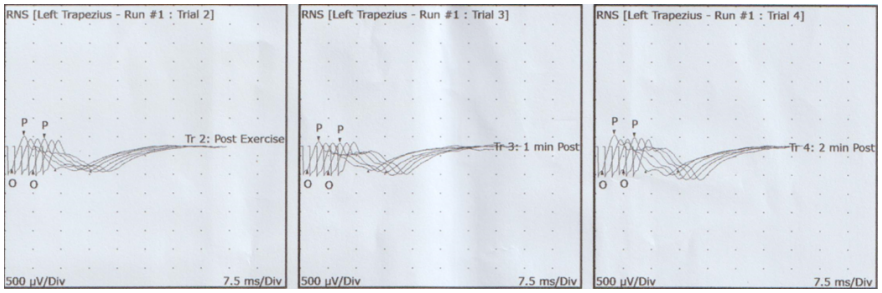
Site	Latency (ms)	Norm	Amplitude (mV)	Norm	CV m/s	Norm	Neg Area ms*mV	Min F-Lat (ms)
Left Facial - Nasalis Motor								
Mastoid	4.0	-	0.51	-			1.86	
Left Median (APB) Motor								
Wrist	3.3	< 4.2	5.9	> 5.0			15.0	24.7
Elbow	7.0	-	5.6	-	54	> 50	14.3	
Left Spinal Accessory Motor								
Neck	1.55	-	0.61	-			2.7	
Left Ulnar (ADM) Motor								
Wrist	2.4	< 4.2	7.9	> 3.0			19.9	25.7
Bel Elbow	5.6	-	6.3	-	63	> 53	15.5	
Abv Elbow	6.8	-	7.4	-	67	> 52	19.5	

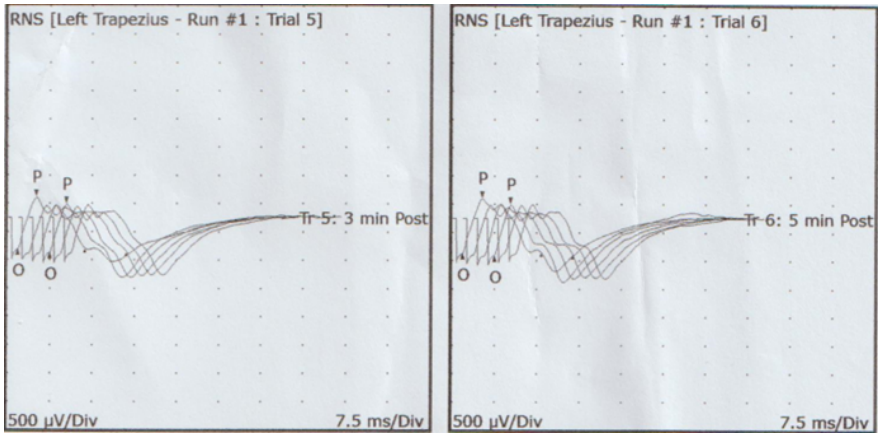
Site	Latency (Onset) (ms)	Latency (Peak) (ms)	Norm	Neg Peak - Start Amp (µV)	Amplitude (P-P) (µV)	Norm	Start CV (m/s)	Norm
Left Median Sensory								
Wrist-Dig II	2.5	3.2	< 3.6	55	74	> 10	56	-
Left Ulnar Sensory								
Wrist-Dig V	2.1	2.8	< 3.7	35	71	> 15	57	-

figure 1: nerve conduction studies showing left spinal accessary and left facial nerves showed low compound muscle action potential (CMAP) amplitudes and post exercise no CMAP amplitudes increments.

Trial #	Label	Amp 1 (mV) O-P	Amp 4 (mV) O-P	Amp % Dif	Area 1 (mV·ms)	Area 4 (mV·ms)	Area % Dif	Rep Rate	Train Length
Left Abductor Digiti Minimi									
Tr 1	Baseline	8.34	8.19	-1.9	23.03	22.45	-2.5	3.00	10
Tr 2	Post Exercise	8.16	8.09	-0.8	23.49	22.42	-4.5	3.00	10
Tr 3	1 min Post	8.41	8.16	-3.0	23.85	22.80	-4.4	3.00	10
Tr 4	2 min Post	8.40	8.14	-3.1	24.53	23.36	-4.8	3.00	10
Tr 5	3 min Post	8.31	7.93	-4.6	24.63	22.78	-7.5	3.00	10
Tr 6	5 min Post	8.26	7.77	-6.0	24.26	22.63	-6.7	3.00	10
Left Nasalis									
Tr 1	Baseline	0.39	0.42	8.7	1.42	1.45	2.4	3.00	10
Tr 2	Post Exercise	0.41	0.42	3.9	1.30	0.00	-100.0	3.00	10
Tr 3	1 min Post	0.43	0.42	-2.6	1.64	1.59	-3.1	3.00	10
Tr 4	2 min Post	0.33	0.34	3.0	1.28	1.24	-3.3	3.00	10
Tr 5	3 min Post	0.40	0.39	-1.7	1.66	1.59	-4.7	3.00	10
Tr 6	5 min Post	0.31	0.33	4.3	1.34	1.35	0.8	3.00	10
Left Trapezius									
Tr 1	Baseline	0.58	0.59	2.1	15.74	16.07	2.1	3.00	10
Tr 2	Post Exercise	0.87	0.84	-4.0	5.06	5.01	-1.0	3.00	10
Tr 3	1 min Post	0.75	0.74	-2.0	5.24	5.80	10.7	3.00	10
Tr 4	2 min Post	0.94	0.85	-10.2	6.30	6.25	-0.9	3.00	10
Tr 5	3 min Post	0.91	0.85	-6.4	6.36	6.83	7.5	3.00	10
Tr 6	5 min Post	0.97	0.89	-8.2	7.14	6.91	-3.1	3.00	10
Tr 7									
Tr 8	High Rate 20Hz	0.39	0.79	103.8	0.00	6.55	0.0	21.10	6

figure 2: Repetitive nerve stimulation (RNS) findings: RNS and exercise testing were performed slow 3 Hz on left ulnar, facial and spinal accessary motor nerves.





javascript:void(0) Figure 3: Repetitive nerve stimulation (RNS) showing significant decrement (>10%) is present on left spinal accessary motor nerve post exercise.

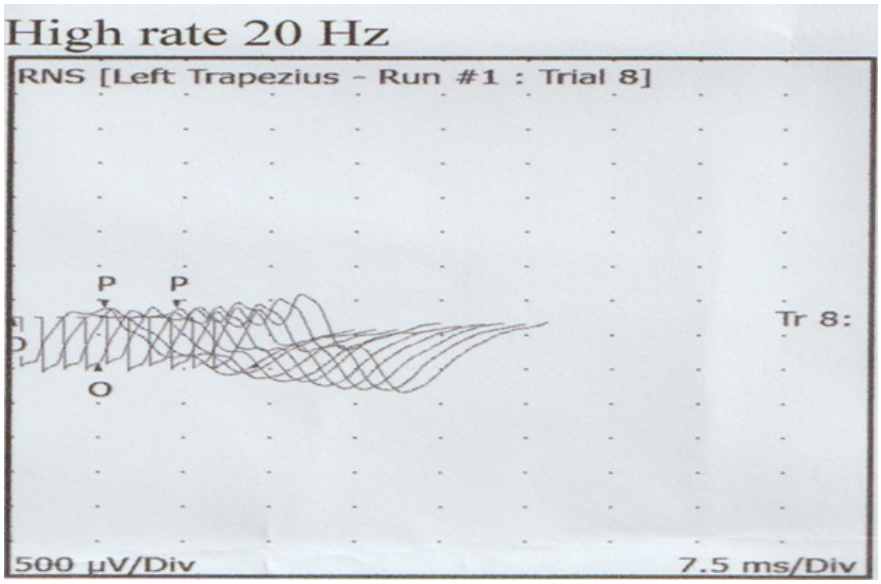


Figure 4: High-frequency (20 Hz) RNS on spinal accessary motor nerve showed significant increment of 103.8% (>100%)

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