Neurology Asia 2024; 29(3) : 843 – 847

Iatrogenic botulism after botulinum toxin type A: Five cases

Özlem Totuk, Ebru Kaya, Esra Nur Sancar, Sena Ayşe Emre, Serkan Demir

University of Health Sciences, Hamidiye Faculty of Medicine, Department of Neurology, Sancaktepe Prof. Dr. Ilhan Varank SUAM, Türkiye.

Abstract

Botulinum toxin A (BTX-A) is frequently used for spasticity, focal dystonia, hemifacial spasm, hyperhidrosis, strabismus, chronic migraine and cosmetic purposes. Therapeutic use is generally safe. It is important to consider the risk of iatrogenic botulism, especially in high dose approved or with unapproved formulations and indications. Five patients with iatrogenic botulism were described. All patient developed systemic symtomps of Botulism following botulinum toxin injection for various reason. Clinical presentatiton, treatment and outcome were explained in this report.
Conclusion: Based on the case series reported, we would like to emphasize the important of adhering to recommended dose of approved formulations approved or unapproved indication of BTX-A.

Keywords: Iatrogenic botulism, botulism, antitoxin.

INTRODUCTION

Botulism is a rare but potentially life-threatening neuroparalytic syndrome caused by toxins produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium commonly found in soil. The neurotoxin binds to receptors on presynaptic nerve terminals and irreversibly blocks the release of the neurotransmitter acetylcholine. There are four main types of botulism according to the mode of transmission: 1. infant botulism, 2. Foodborne botulism, 3. Wound botulism and 4. Rare types (iatrogenic botulism and adult intestinal colonization, the adult form of infant botulism).[1] Botulinum toxin A (BTX-A) is frequently used for spasticity, focal dystonia, hemifacial spasm, hyperhidrosis, strabismus, chronic migraine and cosmetic purposes. Therapeutic use is generally safe. However, if the toxin enters the bloodstream or is administered in high doses, it can lead to life-threatening iatrogenic botulism.[2] Clinical manifestations of botulism typically begin with visual complaints such as blurred vision or diplopia, followed by bilateral cranial neuropathy and then symmetrical weakness. Close monitoring is necessary because of the potential rapid onset of respiratory distress.[3] Autonomic cholinergic symptoms may also occur. Electrophysiologic investigations show borderline or low compound muscle action potential (CMAP) amplitudes, decreased responses with repetitive stimulation and increased with brief exercise or rapid repetitive stimulation, while sensory action potentials are normal. The diagnosis is based on history, clinical evaluation, neurologic examination and may be supported by electrophysiologic findings and serum toxin levels.[2,4] Treatment includes close monitoring, intensive care unit management if necessary, antitoxin administration within the first 48-96 hours[5,6], wound care in case of wound-related botulism, and supportive care.

Here, we present five cases of iatrogenic botulism, a rare cause of botulism.

CASE REPORTS

Patient 1

A 29-year-old woman received subcutaneous botulinum toxin A (BTX-A, Dysport) 600 unit over the axillary region for hyperhidrosis and cosmetic purposes nine days ago. Three days after the injection, the patient presented with complaints of drooping eyelids, cough, dysphagia, generalised muscle weakness and constipation. Neurological examination revealed bilateral ptosis, diplopia in vertical gaze, hypophonia, dysphagia, marked muscle weakness in proximal extremities and neck flexion. Sensory examination was normal. Deep tendon reflexes were hypoactive. Laboratory tests

Address correspondence to: Özlem Totuk, M.D, Department of Neurology, University of Health Sciences, Hamidiye Faculty of Medicine, Sancaktepe Prof. Dr. Ilhan Varank SUAM, Emek Mahallesi, Namık Kemal Cad. No:54, 34785 Sancaktepe / Istanbul, Türkiye. Tel: (0216) 606 33 00, E-mail: totukozlem@gmail.com

Date of Submission: 3 October 2023; Date of Acceptance: 14 May 2024

https://doi.org/10.54029/2024nhi

were unremarkable. While electrophysiological studies show low compound muscle action potential (CMAP) amplitudes in bilateral median and ulnar nerves; Conduction velocities, latencies and sensory nerve conduction studies were found to be normal. Needle electromyography (EMG) revealed denervation potentials over the left deltoid muscle. No changes were observed in the adductor digiti minimi and trapezius muscles with 3 Hz repetitive stimulation, 30 Hz repetitive stimulation or maximal muscle contraction for 10 seconds. Serum acetylcholine receptor antibodies were negative. Serum toxin detection test could not be performed. Iatrogenic botulism was suspected and the patient was hospitalized. Treatment with pyridostigmine 120 mg in divided doses was started, but no clinical response was observed. In view of clinical deterioration, equine heptavalent botulinum antitoxin was administered 14 days after BTX-A injection. Clinical improvement was observed after the second day of antitoxin treatment. The patient was discharged on the eighteenth day of hospitalization. Six-week follow-up showed complete resolution of symptoms. During follow-up, repeated EMG did not show evidence of denervative changes. This case has been previously reported as a case report.[7]

Patient 2

A 36-year-old woman presented with dyspnea and generalised muscle weakness 12 hours following receiving subcutaneous left axillary injection of 200 U Iranian origin botulinum toxin A (BTX-A) for hyperhidrosis. Neurological examination revealed proximal 4/5 muscle strength on the left side. Sensory examination was normal. Deep tendon reflexes were hypoactive. A tendency to use accessory respiratory muscles and tachypnea were observed, indicating that the patient had moderate respiratory distress. Laboratory tests were unremarkable. Electrophysiologic studies revealed prolonged distal latencies and slowed conduction velocities in bilateral median and ulnar sensory nerves. Motor conduction studies were normal. No changes were observed in the adductor digitiminimi muscles with 3 Hz repetitive stimulation or 30 Hz repetitive stimulation or maximal muscle contraction for 10 seconds. The patient was treated with oral pyridostigmine 180 mg in divided doses with minimal improvement and one bottle of equine heptavalent botulinum antitoxin was administered one day after the onset of symptoms. Symptoms almost resolved and the patient was discharged on the second day of hospitalization.

Patient 3

A 44-year-old woman presented with generalised muscle weakness, head drop, difficulty in chewing and swallowing, and difficulty in breathing 5 days following subcutaneous BTX-A (Botox) injections 300 unit to the periorbital, frontal, masseter, cervical, platysma, axillary and bilateral gastrocnemius muscles for cosmetic application. Neurological examination revealed generalised muscle weakness, nasal speech, bilateral weak masseter muscle strength (3/5), marked weakness in eye closure which was more prominent on the right side (3/5), facial myokymia and neck flexion on the right side of the face, and diffuse muscle weakness predominantly in the proximal extremities (4/5). Sensory examination normal. Deep tendon reflexes were hypoactive. Laboratory tests were unremarkable. Electrophysiologic studies showed low compound muscle action potential (CMAP) amplitudes, normal conduction velocities and latencies in bilateral median and ulnar nerves. Sensory nerve studies were normal. No changes were observed in the adductor digiti minimi and trapezius muscles with 3 Hz repetitive stimulation or 30 Hz repetitive stimulation or maximal muscle contraction for 10 seconds. The patient was treated with oral pyridostigmine 180 mg in divided doses with minimal improvment and subsequently given heptavalent botulinum antitoxin. Following that, all the symptoms were completely resolved and the patient was discharged on the tenth day of hospitalization.

Patient 4 and 5

34-year-old married couple received unknown amount of intragastric botulinum toxin (BTX-A, Botox) injection for treatment of obesity. Both of them complaint of blurred vision, slurred speech, dysphagia, respiratory difficulty, fatigue and generalised muscle weakness 2 days after the injection. Neurological examination of female patient revealed bilateral ptosis, nasal speech, bilateral limitation of eyes movements in lateral gaze, weak eyes closure, bilateral weak masseter muscle, weak head flexion and proximal muscle weakness. Her spouse examination revealed similar findings but in lesser degree. Sensory examination was normal. Deep tendon reflexes were hypoactive. Laboratory investigations were unremarkable. The first patients (female) had severe dysphagia which requiring nasogastric tube feeding. Electrophysiological studies performed on the fifth day showed low compound muscle action potential (CMAP) amplitudes, normal

conduction velocities and latencies in bilateral median nerves. Sensory nerve conduction studies were normal. No changes were observed in the adductor digiti minimi and trapezius muscles with 3 Hz repetitive stimulation or 30 Hz repetitive stimulation or maximal muscle contraction for 10 seconds. Electrophysiological study of the male patient were completely normal. Oral pyridostigmine 180 mg in divided doses were prescribed in both cases. In addition to that, first patient was also prescribed methylprednisolone tablet 40 mg in view of respiratory compromised by the treating physician. Both of them showed clinical improvement on the fourth day of admission and discharged well on day eight and ninth of admission. Antitoxin was not administered in these 2 cases as the symptom was rather mild and patients presented on the thirteenth day after the injection.

DISCUSSION

Botulinum toxin is the most potent bacterial toxin. It is known that 5-8% of cases result in death.[5] The Centers for Disease Control and Prevention (CDC) reported 200 cases per year, of which 70-75% are infant botulism, 20-25% are foodborne botulism and 5-10% are wound botulism.[8] Rare causes such as adult intestinal colonization and iatrogenic botulism have only been reported as individual cases. There are four toxin formulations approved by the US Food and Drug Administration (FDA); onabotulinumtoxinA (Botox®), rimabotulinumtoxinB (Myobloc®), abotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®). These are used for therapeutic and cosmetic purposes in conditions such as blepharospasm, strabismus, dystonia, hemifacial spasm, spasticity, hyperhidrosis and chronic migraine. Dysport has a higher tendency to spread to nearby tissues, hence side effects are slightly higher compared to other types of toxin.[9] Side effects are usually transient local pain, hematoma and allergic reactions. However, in rare cases, iatrogenic botulism may occur when the toxin enters the vascular space.[10,11] Iatrogenic botulism is more commonly reported in therapeutic use than in cosmetic use.[10,12,13] The dosage between administrations is believed to differ due to the difference in the range of doses used, with 4-20 units used for cosmetic purposes and up to 300 units used for therapeutic purposes.[14] Both Dysport and Botox are used to treat various muscle contractions and spasms in different areas of the body. Dysport doses range from 500 to 1000 Units for arm and shoulder muscles, up to 1500 Units for leg muscles, up to a maximum of 1000 Units for neck muscles, and up to 120 Units for eye and facial muscles.[14] On the other hand, Botox doses vary from 25 to 300 Units depending on the area being treated, such as eyelid and facial spasms, neck and shoulder contractions, ankle spasms in stroke patients, and excessive sweating in the armpits. Typical doses for specific facial lines include 20 units for vertical lines between the eyebrows, 24 units for lines at the corners of the eyes, and 40 units for forehead lines. If all three facial areas are treated simultaneously, the total dose is 64 units. The dose of BTX-A injection is directly related to the severity of botulism. In some patients, an underlying medical condition such as asthma or cardiac arrhythmia appeared to contribute to the occurrence of botulism. Apart from this, iatrogenic botulism can also be caused by poor injection technique, especially applying near blood vessels.

In one of the patients we followed, botulism developed after overdose, in three after taking an unknown dose, and in one despite taking a dose within therapeutic limits.

Formulation information (onabotulinumtoxinA, rimabotulinumtoxinB, abotulinumtoxinA, incobotulinumtoxinA) was not available for one case.

Two patients received therapeutic BTX-A injections for hyperhidrosis, two for obesity, and one for cosmetic application.

Clinically, there is a common pattern of acute visual complaints followed by bilateral cranial neuropathies and finally bilateral symmetric weakness. Symptoms typically begin in the first to second week after injection. Fever is not observed. Sensory and cognitive functions remain normal except for blurred vision.[15-17] Often in botulism, reflexes may be normal or depressed, depending on the severity of the poisoning.[2] Respiratory symptoms most commonly present as shortness of breath. Intubation and mechanical ventilation may be required. Limb weakness may occur rapidly with respiratory symptoms or alone.[3] Two of our patients initially presented with blurred vision, four had cranial neuropathy and four had generalised symmetrical muscle weakness. Sensory, cognitive functions and reflexes were normal in all cases. Deep tendon reflexes were hypoactive all patients as expected. Four of our patients reported respiratory difficulty, but none require mechanical ventilation.

Cranial nerve dysfunction was present in 93% of cases[3] and caused symptoms such as blurred vision, diplopia, nystagmus, ptosis, dysphagia

and dysarthria due to paralysis of cranial nerves oculomotor, trochlear and abducens. Muscle weakness progresses from the trunk and upper extremities to the lower extremities. Proximal muscles are affected before distal muscles.[2] Autonomic symptoms such as urinary retention and constipation are thought to be related to smooth muscle involvement. Sensory disturbance and paresthesia are rare.

Four of our patients had cranial nerve dysfunction. Four patients exhibited a pattern of muscle weakness. One patient had asymmetric weakness. Sensory function and reflexes were preserved in all cases.

In the absence of secondary infection, blood tests are normal and cerebrospinal fluid (CSF) is typically normal except for rare cases of elevated protein levels.[18] Cranial imaging performed to rule out other possible causes of muscle weakness is normal.

Our patients had normal blood test results. Cerebrospinal fluid (CSF) and cranial imaging were not performed.

Other neuromuscular junction diseases, Guillain-Barre syndrome, brain stem lesions, heavy metal poisoning and polio should be considered in the differential diagnosis.

Although the history and clinical findings did not indicate myasthenia gravis disease, we tested the acetylcholine receptor antibodies in our patient, considering the possibility of an underlying neuromuscular junction disorder, as she showed botulismus despite receiving therapeutic doses of botulinum toxin.

According to the US Centers for Disease Control and Prevention (CDC), botulism investigation is recommended if at least one specific symptom (blurred or double vision, difficulty speaking, voice changes, dysphagia, drooling) and at least one specific sign (ptosis, extraocular palsy, fatigue, decreased eye movements, facial paralysis, loss of expression, poor feeding or sucking, absence of light reflex) are present, along with a paralysis pattern and absence of fever.[19]

Electrophysiologic findings may not be evident in the early stages, but over time abnormalities may be seen in more than 60% of patients.[16] Abnormalities observed include low compound muscle action potential (CMAP) amplitudes, decreasing with slow repetitive stimulation (2-10 Hz), increasing with fast repetitive stimulation (20-50 Hz) or after 10-30 seconds of exercise, Needle electromyography (EMG) shows the presence of short-term low-amplitude motor unit potentials (MUP), signs of active denervation (fibrillation, positive sharp waves) can be seen 2 weeks after onset, and single fiber EMG shows increased vibration and block.[16,17]

CMAP amplitudes decreased in three of our patients, but no abnormality was found with slow and fast repetitive stimulation. Sensory conduction was normal in all cases. Serum toxin level may be performed if the diagnosis is in doubt(20). Since there was no suspicion in our patients' history and clinical picture, no toxin investigation was performed.

The clinical course may vary from a few hours to a few days and may last for months due to irreversible binding to the presynaptic neuromuscular receptor. Recovery usually take part with the development of new nerve terminals.[2]

Treatment includes supportive care, especially close monitoring of respiration, administration of antitoxin[23] and intensive care follow-up.[9] Antitoxin therapy is known to bind to circulating neurotoxins and reduce mortality by preventing toxin binding to the neuromuscular junction.[5] However, data on the efficacy of antitoxin treatment in iatrogenic botulism are limited. Recomended dose for adults is one vial to be administered intravenously.[2,21] It is most effective in the first 48 hours.[2,4,9,10,22] After 48 hours, the risk of allergic response to antitoxin increases. However, antitoxin treatment should be considered in the following days to protect unaffected muscles.[2]

While three patients received antitoxin treatment, two patients were not given antitoxin treatment due to mild symptoms. Patients receiving antitoxin showed rapid clinical improvement.

In conclusion, even when using approved formulations, it is very important to physician to consider iatrogenic botulism, especially when patient received high doses of botulinum toxin of approved or unapproved formulations and indications. BTX-A dosages should be closely monitored. Preventive strategies are recommended as no effective antidote currently available to reverse the effect immidiately.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Freedman M, Armstrong RM, Killian JM, *et al*. Botulism in a patient with jejunoileal bypass. *Ann Neurol* 1986;20(5):641-3. DOI: 10.1002/ana.410200516

2. Rao AK, Sobel J, Chatham-Stephens K, *et al*. Clinical guidelines for diagnosis and treatment of botulism, 2021. *MMWR Recomm Rep* 2021;70(2):1-30. DOI: 10.15585/mmwr.rr7002a1
3. Chatham-Stephens K, Fleck-Derderian S, Johnson SD, *et al*. Clinical features of foodborne and wound botulism: A systematic review of the literature, 1932-2015. *Clin Infect Dis* 2017;66(suppl_1):S11-S16. DOI: 10.1093/cid/cix811
4. Fung HT, Chan KM, Lam SKT. A review on iatrogenicbotulism. *Hong Kong J EmergMed* 2020;27(6):356-67. DOI: 10.1177/1024907920934901
5. O'Horo JC, Harper EP, El Rafei A, *et al*. Efficacy of antitoxin therapy in treating patients with foodborne botulism: A systematic review and meta-analysis of cases, 1923-2016. *Clin Infect Dis* 2017;66(suppl_1):S43-S56. DOI: 10.1093/cid/cix815
6. Yu PA, Lin NH, Mahon BE, *et al*. Safety and improved clinical outcomes in patients treated with new equine-derived heptavalent botulinum antitoxin. *Clin Infect Dis* 2017;66(suppl_1):S57-S64. DOI: 10.1093/cid/cix816
7. Gonul Oner O, Gudek HC, Erturk Cetin O, *et al*. Iatrogenic botulism: A case rreated with botulinum antitoxin. *Clin Neuropharmacol* 2023;46(2):82-4. DOI: 10.1097/WNF.0000000000000535
8. National botulism surveillance. Centers for Disease Control and Prevention. https://www.cdc.gov/botulism/surveillance.html (Accessed on November 16, 2022).
9. SimonettaMoreau M, Cauhepe C, Magues JP, *et al*. A double-blind, randomized, comparativestudy of Dysport vs. Botox in primarypalmarhyperhidrosis. *Br J Dermatol* 2003;149:1041-5. DOI: 10.1111/j.1365-2133.2003.05620.x
10. Coté TR, Mohan AK, Polder JA, *et al*. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol* 2005;53(3):407-15. DOI: 10.1016/j.jaad.2005.06.011
11. Yiannakopoulou E. Serious and long-term adverse events associated with the therapeutic and cosmetic use of botulinum toxin. *Pharmacology* 2015;95(1-2):65-9. DOI: 10.1159/000370245
12. Coban A, Matur Z, Hanagasi HA, *et al*. Iatrogenicbotulismafterbotulinumtoxintype A injections. *ClinNeuropharmacol* 2010;33:158-60. DOI: 10.1097/WNF.0b013e3181d479e0
13. Pena MA, Alam M, Yoo SS. Complications with the use of botulinum toxin type A for cosmetic applications and hyperhidrosis. *Semin Cutan Med Surg* 2007;26(1):29-33. DOI: 10.1016/j.sder.2006.12.004
14. Micromedex Healthcare Series [database]. Greenwood Village, Colo: Micromedex Inc; 1974-2005
15. Lund BM. Foodborne disease due to bacillus and clostridium species. *Lancet* 1990; 336: 983-6.
16. Sanders DB. Electrophysiologic study of disorders of neuromuscular transmission. In: Aminoff MJ, ed: Electrodiagnosis in clinical neurology. 3rd Ed, New York: Churchill LivingstoneInc 1992:347-8.
17. Jubelt B. Merritt's neurology. 2008:259-61.
18. Rao AK, Lin NH, Jackson KA, *et al*. Clinical characteristics and ancillary test results among patients with botulism - United States, 2002-2015. *Clin Infect Dis* 2017; 66(suppl_1):S4-S10. DOI: 10.1093/cid/cix935
19. Rao AK, Lin NH, Griese SE, *et al*. Clinical criteria to trigger suspicion for botulism: An evidence-based tool to facilitate timely recognition of suspected cases during sporadic events and outbreaks. *Clin Infect Dis* 2017;66(suppl_1):S38-S42. DOI: 10.1093/cid/cix814
20. Woodruff BA, Griffin PM, McCroskey LM, *et al*. Clinical and laboratory comparison of Botulism from toxin types A, B and E in the United States, 1975-1988. *J Infect Dis* 1992; 166: 1281-6. DOI: 10.1093/infdis/166.6.1281
21. Hodowanec A, Bleck TP. Clostridiumbotulinum (Botulism). In: Bennett JE, Dolin R, Blaser MJ, Eds: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 8th ed. ElsevierSaunders, Philadelphia. 2015:2763.
22. Souayah N, Karim H, Kamin SS, *et al*. Severe botulism after focal injection of botulinum toxin. *Neurology* 2006;67(10):1855-6. DOI: 10.1212/01.wnl.0000244417.34846.b6
23. Gupta A, Sumner CJ, Castor M. Adult botulism type F in the United States, 1981-2002. *Neurology* 2005; 65: 1694-700. DOI: 10.1212/01.wnl.0000187127.92446.4c