

Case Report

Iatrogenic botulism cases after gastric and axillary application of botulinum toxin and review of literature

Fatma Eser¹, İmran Hasanoğlu¹, Bircan Kayaaslan¹, Ayşe Kaya Kalem¹, Şule Bilen², Gürdal Orhan², Rahmet Güner¹

¹ Ankara Yıldırım Beyazıt University, Ankara City Hospital, Department of Infectious Disease and Clinical Microbiology, Ankara, Turkey

² University of Health Sciences, Ankara City Hospital, Department of Neurology, Ankara, Turkey

Abstract

Introduction: Iatrogenic botulism is a rare, serious disease that progresses with descending paralysis and develops after cosmetic or therapeutic botulinum toxin-A (BoNT-A) application.

Case presentations: In this case series; six cases of iatrogenic botulism followed up in our center are presented. Four of these developed after gastric BoNT-A and two after axillary BoNT-A application.

Results: The most important cause for the disease was the use of unlicensed products and high-dose toxin applications. The first symptoms were blurred vision, double vision, difficulty in swallowing, and hoarseness. Symptoms appeared within 4-10 days after the application of BoNT-A. Symptoms progressed in the course of descending paralysis in the following days with fatigue, weakness in extremities and respiratory distress. Diagnosis was based on patient history and clinical findings. The main principles of foodborne botulism therapy were applied in the treatment of iatrogenic botulism. If clinical worsening continued, regardless of the time elapsed after BoNT-A application, the use of botulinum antitoxin made a significant contribution to clinical improvement and was recommended.

Conclusions: Routine and new indications for BoNT-A usage are increasing and, as a result, cases of iatrogenic botulism will be encountered more frequently. Physicians should be alert for iatrogenic botulism in the follow-up after BoNT-A applications and in the differential diagnosis of neurological diseases that are presented with similar findings.

Key words: botulism; iatrogenic; botulinum toxin; antitoxin.

J Infect Dev Ctries 2024; 18(3):480-487. doi:10.3855/jidc.18868

(Received 10 July 2023 – Accepted 02 September 2023)

Copyright © 2024 Eser *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Iatrogenic botulism is a rare and serious complication of botulinum toxin-type A (BoNT-A) application used for cosmetic or therapeutic purposes. The clinical condition requires early diagnosis, intensive support and treatment [1]. Although unlicensed BoNT-A preparations, inappropriate doses, and applications performed in unqualified health units are responsible factors in the development of iatrogenic botulism, it can also develop in patients where all procedural steps are applied appropriately [2,3]. In this case series, we report six cases of iatrogenic botulism after four gastric and two axillary BoNT-A applications that were indicated for weight loss therapy and hyperhidrosis respectively. A case of iatrogenic botulism after gastric BoNT-A application is presented for the first time in the literature and two of patients are a part of the March 2023 iatrogenic botulism outbreak in Turkey [4,5]. During the follow-up, two patients needed intensive care, and one of them received

invasive mechanical ventilation support. The patients were discharged with recovery and no mortality occurred. The main clinical features of the six patients are presented in Table 1.

Case presentations

Case 1

A 33-year-old female patient was admitted to the emergency department with complaints of new onset of shortness of breath and chest pain. She had complaints of fatigue, weakness in the arms and legs for five days and blurred vision for six days. Physical examination indicated that vital signs were within normal limits. However, neurological examination determined that speech was hypo-phonic and slow; muscle strength of head flexion, arm abduction, shoulder and lower extremity elevations were 3/5; and deep tendon reflexes were normal. Pyridostigmine was administered on the same day following the pre-diagnosis of myasthenia gravis by the neurology department. However, the

expected clinical improvement could not be achieved. One day later, the patient developed dysphagia, diplopia, ptosis, and dyspnea. After that, the patient was followed up in the intensive care unit (ICU) and supported with 2-4 L/min nasal oxygen. When her history was detailed, it was learned that gastric BoNT-A was applied to the patient four days before the visual complaints started. Two vials or 1000 units of botulinum toxin were used in the gastric BoNT-A application procedure. With the pre-diagnosis of iatrogenic botulism, 1 vial (10-22 mL) of botulism antitoxin (BAT) heptavalent was administered to the patient. 12-24 hours after antitoxin administration, regression in diplopia and dysphagia, improvement in speech, improvement in weakness and ptosis were observed. Muscle strength was rated as 5/5. Oxygen support requirement regressed within 24 hours and ventilator support was not needed. The patient was discharged two days after BAT administration. Single fiber electromyography (SFEMG) which was performed 2 days after antitoxin and 3 days after pyridostigmine administration was compatible with motor end plate dysfunction. Complete recovery in all findings was reported at the 8th week telephone visit.

Case 2

A 39-year-old female patient, who underwent gastric BoNT-A application at the same center as the patient in case 1 and on the same day as the first case, presented with complaints of blurred and double vision and hoarseness 10 days after the procedure. Her complaints of blurred and double vision had started 4 days after the procedure and increased gradually. She was admitted to the hospital due to the addition of hoarseness. Physical examination indicated that vital signs were within normal limits, and there was no motor deficit. A vial of BAT was administered to the patient with a pre-diagnosis of iatrogenic botulism. After 12-24 hours, diplopia regressed, dysphagia decreased, and hoarseness improved. Single-fiber electromyography (SFEMG) was performed after 4 days of antitoxin administration, the motor endplate function was normal. During the 8th week outpatient clinic visit, the patient's complaints and findings regressed almost completely.

It was learned that the BoNT-A preparation used in the gastric BoNT-A application procedure of case 1 and case 2 was an unlicensed product. Turkish Medicines and Medical Devices Agency was informed about these cases immediately, and investigations and appropriate interventions were initiated by the agency.

Case 3

A 39-year-old female patient was treated with botulinum toxin 16 days ago due to hyperhidrosis in both axillary regions. The patient presented with muscle weakness that started 9 days after the procedure and gradually increased. She was admitted to the hospital with complaints of weakness of the arms, limitation of abduction and adduction for 7 days, difficulty in swallowing for 4 days, and leg muscle weakness. During neurological examination, neck flexion, hip flexion, extension, and bilateral upper extremity muscle strength were evaluated as 4/5. She could count up to 20 in one breath. Motor endplate function was evaluated as normal with SFEMG that was performed 3 days after antitoxin administration. With the pre-diagnosis of iatrogenic botulism, 1 vial of BAT was administered to the patient. Muscle weakness, limitation of abduction and adduction in the arms, and difficulty in swallowing improved significantly within 48 hours after administration of the antitoxin. It was confirmed that the preparation used as botulinum toxin was a licensed and safe preparation. It was concluded that the clinical situation experienced by the patient was a local unexpected effect of BoNT-A, since botulism symptoms were not typical and her response to BAT treatment was limited.

Case 4

A 34-year-old female patient was admitted to the hospital with weakness in the upper and lower extremities and respiratory distress. The patient, who underwent gastric BoNT-A application 20 days ago, developed blurred vision and headache 4 days after the procedure. She presented to the hospital with an additional complaint of double vision on the 7th day, but she did not receive any diagnosis and treatment. Shortness of breath and respiratory distress developed 16 days after the procedure, and it was diagnosed as pneumonia. The patient was treated with levofloxacin and was discharged after a 1-day follow-up.

Finally, she was presented to the emergency department 20 days after the procedure. Physical examination determined that there was a tendency to sleep, nystagmus in all directions in eye movements, and slowness of speech. During her neurological examination muscle strength of neck flexion was 3/5, upper extremity distal parts were 3/5, proximal parts were 2/5, lower extremities proximal and distal parts were 3/5. Respiratory system examination revealed dyspnea, tachypnea (28/min) and low oxygen saturation (SpO₂: 40%). Thorax computerized tomography (CT) imaging was compatible with aspiration pneumonia.

Respiratory support was started urgently, and she was taken to invasive mechanical ventilator support on the same day, since adequate oxygenation was not achieved with an oxygen mask. One vial of BAT was applied to the patient. Nutrition was provided by a nasogastric tube. The patient was sedated with remifentanyl (0.1 mcg/kg/min IV infusion), and positive inotropic support was not required. The patient received a second dose of BAT 48 hours later. On the 5th day of the intensive care follow-up, the sedation treatment was reduced and stopped. The patient was weaned from invasive mechanical ventilation on the 6th day, and oxygen support was continued with oxygen mask.

During neurological examination performed on the 6th day, muscle strength of neck flexion was 3/5; upper extremity distal parts were 4/5, proximal parts were 3/5; lower extremities proximal and distal parts were 4/5. On the 8th day, the nasogastric tube was removed and oral feeding was provided. The patient was discharged after being followed up in the ICU for 14 days and in the ward for 4 days. Physiotherapy was recommended in the outpatient follow-up. Two weeks later, an

improvement was observed in the upper extremity muscle strength and physical effort capacity findings.

Case 5

A 40-year-old female patient was admitted to the emergency department with complaints of dysphagia and muscle weakness 20 days after gastric BoNT-A application procedure. Her history revealed that ptosis and dysphagia developed 4 days after the procedure, and fatigue and shortness of breath developed 7 days later. It was learned that dyspnea regressed spontaneously within two days. Vital findings during general physical examination were within normal limits, and muscle strength was normal in neurological examination. In addition, she had no visual complaints. Nerve conduction studies were performed to exclude acute polyneuropathy and the results were normal. The patient could tolerate neither repetitive nerve stimulation test nor SFEMG. At the time of the patient's admission, 20 days had passed after gastric BoNT-A application, and there was no progression of complaints and no worsening in physical examination findings.

Table 1. Demographic and clinical characteristics of patients with iatrogenic botulism.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	F	F	F	F	F	F
Age (years)	34	39	31	34	40	38
Weight (kg)	72	90	63	77	93	60
Location of health care center where BoNT-A was administered	Ankara	Ankara	Ankara	Istanbul	Istanbul	Ankara
Botulinum toxin administration date	8 Sep 2022	8 Sep 2022	17 Oct 2022	23 Feb 2023	22 Feb 2023	16 Mar 2023
Indication of BoNT-A application	Weight loss therapy (gastric)	Weight loss therapy (gastric)	Hyperhidrosis (axillary)	Weight loss therapy (gastric)	Weight loss therapy (gastric)	Hyperhidrosis (axillary)
BoNT-A product	Unlicensed	Unlicensed	Licensed	Unknown	Unknown	Unknown
BoNT-A dose (IU)	1000	1000	1000	1500	Unknown	Unknown
Symptom onset	12 Sep 2022	12 Sep 2022	28 Oct 2022	27 Feb 2023	26 Feb 2023	17 Mar 2023
Duration of symptom onset after administration (days)	4	4	11	4	4	1
First symptom	Blurred vision	Blurred vision	Weakness	Diplopia	Dysphagia	Dysphagia
Main symptoms	Fatigue, weakness, shortness of breath	Blurred vision, double vision, hoarseness, weakness, dysphagia	Dysphagia, weakness, difficulty in swallowing	Dysphagia, weakness, fever, shortness of breath	Weakness, ptosis, dysphagia, fatigue, shortness of breath	Fatigue, weakness, hoarseness, shortness of breath
Electromyography (EMG) findings	Motor endplate dysfunction*	Normal motor endplate function [#]	Normal motor endplate function [#]	Could not be performed	Normal motor endplate function	Motor endplate dysfunction
Duration of hospital admission after symptom onset (days)	6	7	5	9	9	1
Usage of botulinum antitoxin	Yes	Yes	Yes	Yes	No	No
Duration of botulinum antitoxin after symptom onset (days)	11	11	16	9	-	-
Pyridostigmine	Yes 60 mg (qid)	No	No	No	Yes 60 mg (tid)	Yes 60 mg (tid)
Intensive care follow-up requirement	Yes	No	No	Yes	No	No

BoNT-A: botulinum toxin-type A; *EMG was performed 2 days after antitoxin and pyridostigmine administration; # EMG was performed 4 days after antitoxin administration; μ EMG was performed 3 days after antitoxin administration; qid: four times a day; tid: three times a day.

Due to this clinical situation BAT treatment was not administered to the patient. She was started on pyridostigmine 60 mg three times a day. Three weeks after the initiation of pyridostigmine therapy, the complaints regressed to a great extent, unfortunately partial fatigue continued.

Case 6

A 38-year-old female patient was admitted with dysphagia and dyspnea. The botulinum toxin was administered to her 25 days ago to both axillary regions due to hyperhidrosis. One day after the procedure, fatigue, weakness in the arm and abdominal muscles, and hoarseness started. In the following days, shortness of breath and weakness in the leg muscles also added to her complaints. In addition, botulinum toxin was applied to the masseter muscle due to clenching two weeks before the procedure for axillary hyperhidrosis.

Upon admission to the hospital, her vital signs and general physical examination were within normal limits. During her neurological examination, lower and upper extremity motor strength was normal, muscle strength of neck flexion was 4/5, and she could count up to 20 in a single breath. SFEMG and repetitive nerve stimulation were performed. Electrophysiological findings were consistent with motor end plate dysfunction. Weakness during swallowing was detected in the swallowing test. Since 25 days had passed after botulinum toxin administration, BAT was not applied. The patient received pyridostigmine (3 x 60 mg/day) treatment. On the 4th day of pyridostigmine treatment, the patient's neck flexion limitation improved, and she could count up to 50 in one breath.

Main clinical features of the six patients were listed in Table 1.

Discussion and review of literature

Botulism is a rare but life-threatening disease caused by the potent toxin produced by *Clostridium botulinum*. Botulinum toxin mostly causes food poisoning following eating of botulinum toxin-containing foods that have been stored improperly. In infant and wound botulism, the disease develops depending on the systemic spread of the toxin after local inoculation. Finally, iatrogenic botulism, which we also observed in this case series, is an unexpected and serious complication of botulinum toxin administrations for therapeutic or cosmetic purposes. Although it is not frequent, case reports and case series are reported intermittently in the literature [6].

Iatrogenic botulism has been reported as case reports since 2003 [7,8]. Research articles including

case series were published from China in 2016 and from Egypt in 2018. Thus, basic information about the clinical features of the disease, diagnosis and follow-up processes were defined [2,9]. As of March 2023, 71 cases have been reported from European countries, especially Turkey and Germany. Thus, this issue has become more important and needs to be emphasized. All 71 cases were patients who received gastric botulinum toxin application in two health care facilities in Turkey [4,10]. Case 4 and case 5 presented in this report were patients who developed iatrogenic botulism after the procedure was performed in these centers.

Iatrogenic botulism develops due to the use of counterfeit or unlicensed botulinum toxin products and/or administration of inappropriate doses of botulinum toxin [9,11,12]. Among the six cases presented here, it was determined that high dose and an unlicensed product were used in the first and second cases in those with gastric BoNT-A application, and high-dose botulinum toxin was used in the fourth case, which required invasive mechanical ventilation support. The dose generally used in gastric application is 200 IU BoNT-A [13,14]. In addition, in gastric botulinum toxin application it is reported that administration at doses of 100, 300, and 500 units have similar weight loss effects and similar clinical outcomes [15]. Based on these data, it was concluded that the use of higher doses of toxin than the standard recommendation and the use of unlicensed products were important factors in the development of the iatrogenic botulism after gastric botulinum application.

Pathophysiology

There are 7 different subtypes (A-G) of botulinum toxin. Botox preparations used for treatment and cosmetic purposes only contain BoNT-A, and this is the subtype responsible for iatrogenic botulism [16,17]. After local injection of botulinum toxin, its local effect begins within 3-7 days and reaches its maximum effect on the 15th day [18]. Depending on the route of entry, its penetration duration into the bloodstream may differ. However, once BoNT enters the circulation, it targets the presynaptic space in the nerve endings. It inhibits muscle contraction by blocking acetylcholine discharge at the synaptic cleft and acetylcholine receptor proteins at the postsynaptic terminal. This blockade is irreversible; recovery and re-contraction can occur after the regeneration of these proteins [6]. The neuron-blocking effect of botulinum toxin usually lasts for four months, and the duration of action is related to the injection site and the dose of the toxin [19].

Clinical features

Iatrogenic botulism diagnosis depends on the patient's history and the presence of clinical findings. Descending bilateral paralysis, which starts with blurred vision and diplopia, primarily affects the cranial nerves and is the typical clinical presentation. It progresses with dysphagia, dysarthria and upper extremity muscle weakness. In severe patients, respiratory distress develops as a result of the respiratory muscles being affected [17].

The diagnostic criteria for botulism to be considered were determined by Rao *et al.* as 1) absence of fever; 2) at least one of the symptoms of “blurred vision, double vision, difficulty speaking, any change in sound of voice, dysphagia, pooling of secretions, thick tongue”; and 3) at least one of the signs of “ptosis, extraocular palsy/fatigability, facial paresis, fixed pupils, descending paralysis beginning with cranial nerves”. Mental status is normal in patients; if there is a change in mental status, other differential diagnoses should be considered [20].

The incubation period in food-borne botulism and wound botulism is 12-72 hours and 5-15 days, respectively. In infant botulism it can be variable and related to different clinical factors. In iatrogenic botulism, the presentation time for clinical findings after the administration of botulinum toxin is longer than in classical botulism types. It was reported that the duration of admission in the hospital was 3-10 days in the Egyptian case series consisting of nine patients [2]. In addition, the duration of admission to the hospital could be extended up to 36 days as reported in the Chinese case series where 86 cases were evaluated [6,9]. In the cases presented in this report, the onset time of symptoms after gastric BoNT-A application procedure was 4 days, and the time to hospital admission was 4-11 days after symptom onset. The onset of symptoms was after 1 and 11 days, and the duration of admission to the hospital was 1 and 5 days after symptom onset in patients who were followed up with suspicion of botulism after axillary BoNT-A injection.

In the case series of iatrogenic botulism, symptoms were reported to be fatigue (86%), blurred vision (84%), dizziness (80%), difficulty in opening eyes (72%), difficulty swallowing (70%), unclear articulation (43%), anxiety, headache, and constipation [9]. Similar with classical botulism, descending bilateral paralysis was the prominent neurologic finding [4,9].

Case 1, case 2, case 4 and case 5 were associated with gastric BoNT-A application. In all these cases,

clinical presentations were compatible with classical botulism symptoms and progression. The symptoms of case 3 started with limited abduction and adduction in the arms, did not progress as typical descending paralysis, and did not have a dramatic response to antitoxin treatment as in other patients. During follow-up of the patient after discharge we agreed, based on our experience, that case 3 was associated with the local side effects of botulinum toxin. Case 6 showed a typical course with descending paralysis; however, the treatment procedure was different from other cases because her admission to hospital was late.

Laboratory tests to detect the presence of botulinum toxin in serum, stool, and gastric fluid, should be performed to confirm botulism. The use of these tests are not recommended for diagnosis because it may cause delay in the diagnosis and worsening of the patient [1]. This general recommendation especially applies to foodborne botulism. When presented with a case of suspected iatrogenic botulism, it may be meaningful to search for toxins only in serum due to differences in botulinum toxin entry route and pathophysiology.

Overall mortality is reported as 5-10% in clinical forms of food-borne and wound botulism [1,17]. In the March 2023 outbreak reported from Turkey, 5 of 66 cases required ICU admission. Fortunately, no mortality was reported in the case series and single case reports for iatrogenic botulism [2,9,17,21-23]. However as indicated in our case 4, the clinical progression could be life-threatening. Regarding case 4, it should be emphasized that early diagnosis and administration of antitoxin was a life-saving approach, and should be applied to patients with iatrogenic botulism.

SFEMG is considered the most sensitive method for diagnosing neuromuscular junction (NMJ) disorders such as myasthenia gravis. It is also sensitive in detecting early modifications at the NMJ due to BoNT-A administration. Very early jitter increase has been reported in many publications with a mean of days 15 to 30 (a peak on day 7 or earlier after injection) [18]. While increased jitter was observed in two of our cases supporting NMJ dysfunction, SFEMG could not be performed in one case because the patient could not tolerate it, and NMJ function was normal in 3 cases. In our cases, SFEMG was applied within the first 30 days after botulinum toxin applications. Ruet *et al.*, reported abnormal SFEMG in 75% of the group which they evaluated as pseudobotulism, while they found a similar rate in the group they evaluated as botulism [24]. In our cases, abnormality was found in two of the 5 cases in which SFEMG could be performed. However, our case

number is insufficient to comment on SFEMG abnormalities in iatrogenic botulism.

Neurologically differential diagnosis is important and sometimes difficult for iatrogenic botulism diagnosis. The diseases of acute polyneuropathies, food botulism, myasthenia gravis, and cerebrovascular events must be considered in the patients who are admitted to hospital with signs of bulbar involvement, extremity weakness and descending paralysis findings. In case 1, the first diagnosis after admission of the hospital was myasthenia gravis. When clinical response could not be obtained, it was investigated in the differential diagnosis and clinical anamnesis was detailed and learned that gastric BoNT-A was applied in the patient's history. The questioning of the application of BoNT-A, especially in patients presenting with these symptoms and neurological findings, should be added to our routine check in the patient's anamnesis. On the other hand, it is reported that the use of BoNT-A may cause aggravation and should be diagnosed in patients with subclinical myasthenia gravis [3,22,25,26].

Treatment

Botulism treatment consists primarily of BAT administration, neurological and respiratory close follow-up, and supportive treatment [27]. Guidelines and clinical studies generally give recommendations for food-borne, wound, or infant botulism. It is also appropriate to administer these approaches for iatrogenic botulism.

The patients with suspected iatrogenic botulism should be hospitalized, examined for necessary vital signs, and considered for antitoxin administration. It is recommended that patients be followed up in a center where respiratory support, airway control, and invasive mechanical ventilation can be rapidly administered when necessary. While planning the antitoxin treatment, the relevant public health centers should be informed and BAT is received from the centers. It is recommended to administer antitoxin to patients with suspected botulism. Antitoxin may not be required if the patient's symptoms are mild, are not expected to progress to paralysis in the future, or the patient requires respiratory support [1].

Antitoxin administration for our patients were planned in line with these recommendations. At the time of hospital admission, antitoxin was administered due to the progression of neurological findings and necessity of respiratory support for the first and fourth cases, and the progression of the neurological findings in the second case. Significant clinical improvement

was achieved in 12 to 24 hours in all three patients. In case 3, antitoxin was administered due to the progression of neurological findings, although muscle weakness and neurological progression were not typical of classical botulism. The presence of clinical response in this patient was not as clear as in other patients who received the antitoxin. In the follow-up outpatient clinic examinations, it was concluded that the situation was related to the local effects of botulinum toxin. Cases 5 and 6 were followed up without antitoxin administration, since they presented late and did not have clinical progression upon admission to the hospital.

Administration of antitoxin therapy as early as possible after BoNT exposure is the most important factor for clinical response to therapy. In cases of iatrogenic botulism, diagnosis and initiation of antitoxin therapy could take up to two weeks. In the case series and single case reports, administration day of botulinum antitoxin, for iatrogenic botulism after symptom onset has been reported as ranging from 5 to 15 days. However, positive results were obtained in terms of stopping the clinical worsening of the patients and clinical improvement in the cases of iatrogenic botulism, even when they were given antitoxin therapy at delayed days after BoNT applications [2,21,28,29].

The botulinum antitoxin product is a heptavalent equine serum antitoxin including antitoxins against A-G serotypes. In iatrogenic botulism, the responsible toxin for the disease is only serotype A. However, monovalent antitoxin is not currently usable, so all the patients receive the heptavalent antitoxin. Around 1-5% patients have reported side effects, mostly hypersensitivity, fever, bradycardia, tachycardia, hypertension and rarely anaphylaxis. There were no side effects observed in our four patients who were administered the botulinum antitoxin.

Pridostigmine is an approved reversible acetylcholine esterase inhibitor for the treatment of myasthenia gravis. It is known that pyridostigmine can also reduce the cholinergic side effects that may occur after botulinum toxin applications [30,31]. Pyridostigmine was administered 3-4 times a day to our cases for treatment and symptomatic improvement was achieved. In previous cases, pyridostigmine was used for the treatment of iatrogenic botulism and contributed to clinical improvement [21,23].

Conclusions

Health care units will likely come across iatrogenic botulism cases more frequently as a result of the increasing use of botulinum toxin in both therapeutic

and cosmetic indications. Although botulinum toxin injections are generally safe applications, inappropriate dose, unlicensed preparation, or procedure inconsistencies can cause iatrogenic botulism, which could have serious clinical outcomes. After BoNT-A applications, patients should be advised in terms of their symptoms and physicians should be careful in terms of this adverse event. On the other hand, botulinum toxin applications should be carefully questioned in the differential diagnosis of patients with signs of descending paralysis such as blurred vision, hoarseness, weakness in the upper extremities, and respiratory distress. The diagnosis of iatrogenic botulism is based on the presence of clinical findings and anamnesis. In case of suspicion of the disease, patients should be closely monitored and followed up in a center where intensive care support can also be provided. If the progression of clinical signs continues, antitoxin therapy contributes to clinical improvement and is recommended. In addition, the health authorities who are responsible for the use of drugs and the application of the procedure should be informed about the adverse event, and precautions should be taken to avoid epidemic situations.

Authors' contributions

Conceptualization: FE, RG; methodology: FE, SB; writing – original draft preparation: FE, SB, IH, BK; writing – review and editing: FE, SB, IH, AK, GO, RG; clinical follow up of cases: FE, IH, BK, AK, SB, GO, RG; supervision: FE, BK, RG.

References

- Rao AK, Sobel J, Chatham-Stephens K, Luquez C (2021). Clinical guidelines for diagnosis and treatment of botulism, 2021. *MMWR Morb Mortal Wkly Rep* 70: 1-30. doi: 10.15585/mmwr.mm7002a1.
- Rashid EAMA, El-Mahdy NM, Kharoub HS, Gouda AS, ElNabarawy NA, Mégarbane B (2018). Iatrogenic botulism outbreak in Egypt due to a counterfeit botulinum toxin A preparation - a descriptive series of patient features and outcome. *Basic Clin Pharmacol Toxicol* 123: 622-627. doi: 10.1111/bcpt.13048.
- Timmermans G, Depierreux F, Wang F, Hansen I, Maquet P (2019). Cosmetic injection of botulinum toxin unmasking subclinical myasthenia gravis: a case report and literature review. *Case Rep Neurol* 11: 244-251. doi: 10.1159/000502350.
- World Health Organization (2023) Iatrogenic botulism - European region. Available: <https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON450>. Accessed: 8 June 2023.
- Dorner MB, Wilking H, Skiba M, Wilk L, Steinberg M, Worbs S, Çeken S, Kaygusuz S, Simon S, Becher F, Mikolajewska A, Kornschöber C, Büttler T, Jourdan-Da-Silva N, An der Heiden M, Schaade L, Stark K, Dorner BG, Frank C (2023). A large travel-associated outbreak of iatrogenic botulism in four European countries following intragastric botulinum neurotoxin injections for weight reduction, Türkiye, February to March 2023. *Euro Surveill* 28: 2300203. doi: 10.2807/1560-7917.ES.2023.28.23.2300203.
- Jeffery IA, Karim S (2023) Botulism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. PMID: 29083673. Available: <https://www.ncbi.nlm.nih.gov/books/NBK459273/>. Accessed: 8 August 2023.
- Beseler-Soto B, Sánchez-Palomares M, Santos-Serrano L, Landa-Rivera L, Sanantonio-Valdearcos F, Paricio-Talayero JM (2003) Iatrogenic botulism: a complication to be taken into account in the treatment of child spasticity. *Rev Neurol* 37: 444-446. doi: 10.33588/rn.3705.2003250.
- Chertow DS, Tan ET, Maslanka SE, Schulte J, Bresnitz EA, Weisman RS, Bernstein J, Marcus SM, Kumar S, Malecki J, Sobel J, Braden CR (2006) Botulism in 4 adults following cosmetic injections with an unlicensed, highly concentrated botulinum preparation. *JAMA* 296: 2476-2479. doi: 10.1001/jama.296.20.2476.
- Bai L, Peng X, Liu Y, Sun Y, Wang X, Wang X, Lin G, Zhang P, Wan K, Qiu Z (2018). Clinical analysis of 86 botulism cases caused by cosmetic injection of botulinum toxin (BoNT). *Medicine* 97: e10659. doi: 10.1097/MD.00000000000010659.
- Mohapatra RK, Mishra S, Tuglo LS (2023). Surge in iatrogenic botulism cases in Europe: threat perceptions and salient countering measures. *New Microbes New Infect* 53: 101142. doi: 10.1016/j.nmni.2023.101142.
- Czerwiński M, Czarkowski MP, Kondej B (2018). Foodborne botulism in Poland in 2016. *Przegl Epidemiol* 72: 149-155. doi: 10.32394/pe.72.4.19.
- Rao AK, Lin NH, Jackson KA, Mody RK, Griffin PM (2017). Clinical characteristics and ancillary test results among patients with botulism - United States, 2002-2015. *Clin Infect Dis* 66 Suppl 1: S4-S10. doi: 10.1093/cid/cix935.
- Sánchez-Torralvo FJ, Vázquez-Pedreño L, Gonzalo-Marín M, Tapia MJ, Lima F, García-Fuentes E, García P, Moreno-Ruiz J, Rodríguez-Cañete A, Valdés S, Oliveira G (2022) Endoscopic intragastric injection of botulinum toxin A in obese patients accelerates weight loss after bariatric surgery: follow-up of a randomised controlled trial (IntraTox Study). *J Clin Med* 11: 2126. doi: 10.3390/jcm11082126.
- Özdil K, Çağatay AK, Sayar S, Aykut H, Kılıç ET (2022). Can gastric botulinum toxin A injection be used as minimally invasive procedure in the short-term treatment of obesity? *J Minim Access Surg* 18: 201-206. doi: 10.4103/jmas.JMAS_105_21.
- Topazian M, Camilleri M, Enders FT, Clain JE, Gleeson FC, Levy MJ, Rajan E, Nehra V, Dierkhising RA, Collazo-Clavell ML, Talley NJ, Clark MM (2013) Gastric antral injections of botulinum toxin delay gastric emptying but do not reduce body weight. *Clin Gastroenterol Hepatol* 11: 145-150.e1. doi: 10.1016/j.cgh.2012.09.029.
- O'Horo JC, Harper EP, El Rafei A, Ali R, DeSimone DC, Sakusic A, Abu Saleh OM, Marcelin JR, Tan EM, Rao AK, Sobel J, Tosh PK (2017) Efficacy of antitoxin therapy in treating patients with foodborne botulism: a systematic review and meta-analysis of cases, 1923-2016. *Clin Infect Dis* 66 Suppl 1: S43-S56. doi: 10.1093/cid/cix815.

17. World Health Organization (2023) Botulism. Available: <https://www.who.int/news-room/fact-sheets/detail/botulism>. Accessed: 2 April 2023.
18. Moron H, Gagnard-Landra C, Guiraud D, Dupeyron A (2021) Contribution of single-fiber evaluation on monitoring outcomes following injection of botulinum toxin-A: a narrative review of the literature. *Toxins* 13: 356. doi: 10.3390/toxins13050356.
19. Flynn TC (2010) Botulinum toxin: examining duration of effect in facial aesthetic applications. *Am J Clin Dermatol* 11: 183-199. doi: 10.2165/11530110-000000000-00000.
20. Rao AK, Lin NH, Griese SE, Chatham-Stephens K, Badell ML, Sobel J (2017) 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* 66 Suppl 1: S38-S42. doi: 10.1093/cid/cix814.
21. Gonul Oner O, Gudek HC, Erturk Cetin O, Demir S (2023) Iatrogenic botulism: a case treated with botulinum antitoxin. *Clin Neuropharmacol* 46: 82-84. doi: 10.1097/WNF.0000000000000535.
22. Durmuş Tekçe H, Deymeer F, Oflazer Serdaroğlu P, Parman Y (2016) Myasthenia gravis after botulinum toxin type A injection. *Turkish J Neurol* 22: 143-144. doi: 10.4274/tnd.02703.
23. Coban A, Matur Z, Hanagasi HA, Parman Y (2010). Iatrogenic botulism after botulinum toxin type A injections. *Clin Neuropharmacol* 33: 158-160. doi: 10.1097/WNF.0b013e3181d479e0.
24. Ruet A, Durand MC, Denys P, Lofaso F, Genet F, Schnitzler A (2015) Single-fiber electromyography analysis of botulinum toxin diffusion in patients with fatigue and pseudobotulism. *Arch Phys Med Rehabil* 96: 1103-1109. doi: 10.1016/j.apmr.2015.01.010.
25. Dressler D (2010) Subclinical myasthenia gravis causing increased sensitivity to botulinum toxin therapy. *J Neural Transm Vienna* 117: 1293-1294. doi: 10.1007/s00702-010-0481-9.
26. Glick ZR, Vaphiades MS, Northington ME (2013). OnabotulinumtoxinA unmasking myasthenia gravis. *Dermatol Surg* 39: 472-473. doi: 10.1111/dsu.12022.
27. Sobel J, Rao AK (2017) Making the best of the evidence: toward national clinical guidelines for botulism. *Clin Infect Dis* 66 Suppl 1: S1-S3. doi: 10.1093/cid/cix829.
28. Fan KL, Wang YL, Chu G, Leung LP (2016). Delayed antitoxin treatment of two adult patients with botulism after cosmetic injection of botulinum type A toxin. *J Emerg Med* 51: 677-679. doi: 10.1016/j.jemermed.2016.07.097.
29. Sheth AN, Wiersma P, Atrubin D, Dubey V, Zink D, Skinner G, Doerr F, Juliao P, Gonzalez G, Burnett C, Drenzek C, Shuler C, Austin J, Ellis A, Maslanka S, Sobel J (2008) International outbreak of severe botulism with prolonged toxemia caused by commercial carrot juice. *Clin Infect Dis* 47: 1245-1251. doi: 10.1086/592574.
30. Rouiantan A, Alizadeh Otaghvar H, Mahmoudvand H, Tizmaghz A (2019). Rare complication of botox injection: a case report. *World J Plast Surg* 8: 116-119. doi: 10.29252/wjps.8.1.116.
31. Young DL, Halstead LA (2014) Pyridostigmine for reversal of severe sequelae from botulinum toxin injection. *J Voice* 28: 830-834. doi: 10.1016/j.jvoice.2014.04.010.

Corresponding author

Fatma Eser, MD
Ankara City Hospital, Neurology Orthopedics Hospital,
B1/E/7 Üniversiteler Mah. Bilkent, Ankara, Turkey.
Tel: 03125960000- 521324, 05079921101
Fax: 0312 552 99 99
Email: fatmacevelekeser@hotmail.com

Conflict of interests: No conflict of interests is declared.