



Case report

A severe case of iatrogenic botulism associated with COVID-19 infection

Qian Ma, Guang-Jing Liu^{*}, Shuang Wang, Wen-Di Wang, Ning Liu, Che-Jiang Wang, Xiao-Bing Li

Department of Plastic and Burn, Tianjin First Center Hospital Affiliated to Nankai University, Tianjin, 300000, China

ARTICLE INFO

Keywords:

Botulism
Botulinum toxin
COVID-19 infection
Plastic surgery injection
Respiratory failure

ABSTRACT

Background: The botulinum toxin is an extremely potent substance that impacts the nervous system. There has been a rise in cases of medical poisoning associated with it, particularly in the field of plastic and aesthetic procedures, in recent years.

Case description: A 51-year-old woman underwent a facial wrinkle reduction procedure with an unauthorized injection of 100 U of botulinum toxin at an unlicensed medical facility six days prior to hospitalization. Over time, her toxicity symptoms intensified, impacting her respiratory muscles, and she did not receive antitoxin treatment. She was concurrently diagnosed with a COVID-19 infection during this period. Nonetheless, she experienced a full recovery 86 days after the injection.

Conclusion: Currently, there is no effective antidote for botulism. Nevertheless, the timely administration of antitoxin can contribute to reducing the duration of the illness, alleviating symptoms, and preventing its recurrence. It is essential to recognize that individual responses may vary, and in this instance, the absence of antitoxin treatment did not significantly prolong the course of the disease. Accurate diagnosis of medical poisoning can be based on injection history and clinical symptoms. Early indications like fatigue and dry mouth warrant particular attention, emphasizing the importance of immediate medical intervention. To address emergencies, the Center for Disease Control (CDC) should maintain an accessible supply of antitoxin. Patients with severe poisoning should be hospitalized until their respiratory muscle strength is fully restored.

1. Background

Type A botulinum toxin injections are also commonly employed in cases of medical poisoning. The botulinum toxin is a neurotropic toxin that operates at the nerve-muscle junction by inhibiting the release of acetylcholine into the synaptic cleft. Consequently, this inhibition disrupts the transmission of signals between the nerve and muscle, leading to muscle paralysis [1]. Crucially, this paralysis does not directly harm the nerves or muscles, and its effects are reversible. Botulism can be categorized into three levels [2]. Mild cases typically manifest symptoms related to the eye muscles, such as ptosis, blurred vision, double vision, inability to close the eyes, sensitivity to light, strabismus, vision loss, and delayed light reflex. Headaches, general weakness, and, in some instances, vomiting and diarrhea may also be present. Moderate cases, in addition to the previously mentioned symptoms, may involve oropharyngeal muscles,

^{*} Corresponding author. Department of Plastic and Burn, Tianjin First Center Hospital Affiliated to Nankai University, No. 24 of Fukang Road, Hexi District, Tianjin, 300000, China.

E-mail address: liuguangjinglj@126.com (G.-J. Liu).

<https://doi.org/10.1016/j.heliyon.2024.e32237>

Received 4 March 2024; Received in revised form 29 May 2024; Accepted 30 May 2024

Available online 31 May 2024

2405-8440/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

leading to difficulties in swallowing, choking, barylalia, salivation, and other symptoms. Severe cases, although rare, may exhibit respiratory muscle involvement, resulting in dyspnea, chest tightness, breathlessness, symptoms of respiratory failure, and life-threatening indicators. In recent years, the increased utilization of botulinum toxin in plastic and aesthetic treatments has contributed to a growing number of patients experiencing clinical medical poisoning. However, reports of severe cases remain limited. This particular case coincided with the COVID-19 epidemic in China during the patient's hospitalization for a COVID-19 infection. The patient ultimately recovered and was discharged from the hospital, prompting the reporting of this case.

2. Case description

The patient in question, a 51-year-old woman with a previously clean health record and no known allergies, was hospitalized due to a progressive weakening of eye opening, ptosis, and eyelid swelling over the course of three days. She also encountered difficulties in speech, trouble swallowing, and weakness in raising her upper limbs, which developed over a two-day period. Additionally, she reported dryness in the throat, shortness of breath, and an increased heart rate for a day. These symptoms continued to worsen. Six days before seeking medical attention, the patient received subcutaneous injections of 100 U of A-type botulinum toxin in the forehead, bilateral periocular region, and temporal wrinkle areas from an informal source at an unofficial medical facility. Subsequent to the injections, she progressively developed difficulties in eye opening, ptosis, and eyelid swelling. Two days later, speech impediments, dysphagia, and weakness in raising both upper limbs manifested. A day before admission to our department, the patient reported oropharyngeal dryness, respiratory distress, and an accelerated heartbeat. Previous treatments with rehydration solution, dexamethasone, sodium creatine phosphate, and other medications at different hospitals in the city did not yield improvement; instead, her symptoms continued to deteriorate. Upon admission to our department, she underwent a thorough examination at the hospital. Upon examination, she exhibited lucid consciousness, proper development, moderate nutrition, an absence of yellowish skin discoloration, no skin rash or hemorrhagic spots, and non-palpable superficial lymph nodes. She presented with ptosis and edema, although her conjunctiva appeared normal. No cyanosis was observed in the lips and mouth, and the tongue was centrally positioned. The neck displayed softness and non-resistance, with no positive indications noted during the cardiopulmonary and abdominal examinations. She faced challenges in raising her head and upper limbs, experiencing muscle strength graded at 4 in the limbs. No signs of hyper-reflexia or weakness were evident in bilateral Achilles, knee, and tendon reflexes, and no pathological signs were identified. The results of the blood tests revealed hemoglobin at 107 g/L, potassium at 3.43 mmol/L, sodium at 131.8 mmol/L, calcium at 2.11 mmol/L, alanine aminotransferase at 9 U/L, aspartate aminotransferase at 17.1 U/L, albumin at 41.1 g/L, creatinine at 50 μ mol/L, lactate dehydrogenase at 120 U/L, creatine kinase at 85.4 U/L, and cholinesterase at 6665.5 U/L. Both cranial CT and chest CT scans did not reveal any apparent abnormalities, while cardiac B-ultrasound indicated mild pulmonary hypertension and a small amount of pericardial effusion. The patient refused the Electromyography. Based on the consensus regarding the diagnosis of botulinum toxin injection poisoning, considering the patient's medical history, physical signs, and the results of the medical examination, the diagnosis of A-type botulism was confirmed.

After the patient's admission to the hospital, she underwent cardiac monitoring, strict bed rest, oxygen therapy, gastric tube insertion, energy supplementation, nutritional support, and various other supportive treatments. The hospital reached out to the local CDC department and the Health and Wellness Committee to request the antitoxin, but unfortunately, the patient did not receive this treatment. Eight days post-injection, her symptoms persisted and intensified, including self-aware breathlessness, dyspnea, limb muscle strength graded at 2+, the presence of tendon reflexes, and the absence of pathological signs. The patient received high-flow oxygen and was transferred to the Department of Intensive Care Medicine for further care. Airway management, including positional changes and back patting, was administered. On the 9th day post-injection, the patient developed a small pericardial effusion and mild pulmonary hypertension. By the 10th day post-injection, the patient experienced a significant drop in oxygen saturation, resulting in unconsciousness. A tracheal tube was connected to a ventilator to aid in respiration, leading to the patient regaining consciousness. By the 13th day post-injection, limb muscle strength reached level 2+. On the 19th day post-injection, a tracheotomy was performed, and assisted ventilation continued. During this time, the patient developed a lung infection caused by *Pseudomonas aeruginosa*, which was stabilized through anti-infective treatment with piperacillin sodium and sulbactam sodium for injection. The patient remained bedridden, and Chinese medicine massage was administered to prevent joint rigidity. On the 33rd day post-injection, the patient tested positive for COVID-19, as confirmed by the nucleic acid test, exhibiting symptoms of fever and cough. The patient orally took combined tablets of nirmatrelvir and ritonavir. By the 37th day post-injection, the COVID-19 nucleic acid test turned negative. Muscle strength rebounded for the first time on the 34th day post-injection, with limb muscle strength assessed at grade 3-. By the 37th day post-injection, limb muscle strength had reached grade 3. On the 45th day post-injection, the patient experienced a rebound in muscle strength, and spontaneous respiration was observed. Despite facing breathing difficulties after the ventilator was removed, the patient and family insisted on leaving the hospital with self-administered respiratory assistance. However, on the 61st day post-injection, the patient was readmitted due to dyspnea. Upon examination, limb muscle strength was graded at 4, and the Brudzinski sign was negative. The patient received ventilator support in SIMV mode, airway management, intermittent sputum suction, citicoline, and mecobalamin for nerve nutrition. Traditional Chinese massage was also administered to enhance joint mobility. During treatment, the patient gradually transitioned to intermittent CPAP mode for independent breathing exercises. By the 69th day post-injection, the patient was successfully weaned off the ventilator and switched to high-flow oxygen therapy. At the 86th day post-injection, the patient achieved independent breathing without oxygen support and without respiratory distress. Blood gas analysis showed normal results, leading to the patient's discharge after a thorough hospital evaluation.

3. Discussion

Cases of medical poisoning are infrequent and rely on the establishment of a standardized system for managing toxic and anesthetic drugs. The lethal dose of botulinum toxin ranges from 2,500 to 3,500 IU [3], and it is recommended not to exceed an injection dose of 500 IU [4]. In the context of aesthetic injections in clinical practice, the typical dosage ranges from 30 to 200 IU, significantly below the lethal dose for a 70 kg adult. Instances of medical poisoning primarily occur in individuals with an allergic reaction to the toxin or in cases of unauthorized botulinum toxin injections at informal institutions. According to Li, the labeled dose of botulinum toxin from unknown sources, when administered by informal institutions, may lack reliability. Its actual potency could be much higher, possibly dozens or even hundreds of times greater than the labeled dose [5]. Injecting what is considered a safe dose could easily result in serious medical complications such as respiratory failure, blurred vision, dysphagia [6,7], and other poisoning-related issues.

The positivity rate of botulinum toxin serologic examination is relatively low [8], making laboratory tests an unreliable diagnostic basis. However, diagnosing medical poisoning is often more straightforward compared to food-borne poisoning. Patients typically present with a clear history of botulinum toxin injection, occurring 1–10 days before the onset of the disease, followed by a series of clinical symptoms such as dry mouth, fatigue, ptosis, choking while drinking water, difficulty in swallowing, dysphagia, and more. In this case, the patient adhered to the typical incubation cycle, had a well-defined injection history, and displayed clinical manifestations of dyspnea and respiratory failure, aligning with the diagnosis of severe botulism. The systemic symptoms resolved three months after the disease onset, consistent with the typical duration of botulinum toxin effectiveness (3–4 months) and reported recovery times for patients with severe toxicity in the literature [2]. A shorter incubation period is associated with increased disease severity. Following the peak phase, symptoms gradually diminish. The recovery of muscle strength follows a specific pattern, with improvements in respiratory, swallowing, and speech difficulties occurring first, followed by the gradual restoration of other muscle paralysis [4]. Visual acuity recovery is slower, sometimes spanning several months. In this particular case, the restoration of respiratory muscle function occurred later than the recovery of limb muscle strength, which deviates from the pattern described in the literature.

The standard treatment for botulism typically involves the early administration of antitoxin, especially within the initial 2 days of symptom onset. This approach has demonstrated efficacy in shortening the disease course, reducing mortality [9], improving symptoms, preventing disease recurrence, and influencing disease severity and prognosis [4,5,10]. Additionally, providing symptomatic support is crucial to prevent complications. The early use of antitoxin has the potential to delay and halt disease progression. Even if early administration is not feasible, it should be initiated as soon as possible, as it can still mitigate the severity of poisoning symptoms and shorten their duration [11]. In this particular case, the patient did not receive antitoxin due to its unavailability, and the recovery time did not differ significantly from the previously documented duration. The patient's family insisted on her premature discharge from the hospital, leading to readmission with recurring symptoms and respiratory failure. The connection between the recurrence of symptoms and the absence of antitoxin administration remains uncertain. It is also hypothesized that the overall recovery time could potentially have been shortened with the timely administration of antitoxin.

During the patient's hospitalization amid the COVID-19 epidemic, she subsequently tested positive for the virus. The patient underwent standard antiviral therapy and yielded a negative test result one week later. Symptoms typical of a COVID-19 infection, such as fever and cough, manifested during the viral infection period. While there were no apparent signs of pneumonia, the patient's limb muscle strength seemingly experienced a rebound when assessed on the second day after the viral infection. Consequently, it cannot be conclusively determined whether the COVID-19 infection had a corresponding impact. Additionally, prior reports have suggested that in cases of botulism, the recovery time for respiratory muscles tends to precede that of limb muscles. However, in this patient's case, the restoration of limb muscle strength occurred prior to that of the respiratory muscles. It cannot be ruled out that the COVID-19 infection might have influenced respiratory function.

The increased prevalence of medical botulinum toxin poisoning is attributed to the widespread application of botulinum toxin in plastic aesthetic procedures and the emergence of non-standardized practices. A definitive diagnosis can be established by considering the patient's history of botulinum toxin injections alongside typical clinical symptoms. It is essential to pay careful attention to early indicators like fatigue and dry mouth to ensure prompt medical intervention and prevent the escalation of conditions to a severe stage. The recovery of patients heavily relies on standardized treatment, timely administration of antitoxin, and the implementation of comprehensive life support measures.

4. Conclusions

At present, botulinum neurotoxin antitoxin serves as the antidote for botulism, and its timely administration is crucial. Although it cannot reverse symptoms, it effectively neutralizes circulating toxins, reducing illness duration and severity. However, its availability may vary, posing challenges in management. For instance, in our case, the lack of routine availability of botulinum antitoxin from the local disease control department prevented its use, underscoring the importance of preparedness and access to antidotes in managing iatrogenic botulism effectively.

The increase in cases of medical botulism is linked to its application in plastic surgery. A clear diagnosis of this condition can be made by evaluating the patient's history of botulinum toxin injections and recognizing typical clinical symptoms. Taking this condition seriously is crucial, and early medical intervention should be pursued upon the detection of mild symptoms like fatigue and dry mouth.

Antitoxin should be readily available for emergency treatment at local medical facilities and CDC departments.

Hospitalization of patients with severe poisoning is recommended until their respiratory muscle strength is completely regained, aiming to prevent potential serious complications like respiratory failure after discharge.

Ethics approval and consent to participate

This study was conducted with approval from the Ethics Committee of Tianjin First Center Hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent for the publication of all images, clinical data and other data was obtained from all participants.

Consent for publication

All participants signed a document of informed consent.

Funding

This study was funded by the General Scientific and Technological Projects of Tianjin Health and Wellness Committee (Grant Number: TJWJ2022MS016). The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CRedit authorship contribution statement

Qian Ma: Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Guang-Jing Liu:** Writing – review & editing, Supervision, Conceptualization. **Shuang Wang:** Writing – review & editing, Investigation, Conceptualization. **Wen-Di Wang:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **Ning Liu:** Writing – review & editing, Project administration, Conceptualization. **Che-Jiang Wang:** Writing – review & editing, Software, Resources, Conceptualization. **Xiao-Bing Li:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to acknowledge the hard and dedicated work of all the staff who implemented the intervention and evaluation components of the study.

References

- [1] C.H. Chalk, T.J. Benstead, J.D. Pound, Medical treatment for botulism, *Cochrane Database Syst. Rev.* 4 (4) (2019), <https://doi.org/10.1002/14651858.cd008123.pub4>.
- [2] Y. Dong, J.B. Tang, Y.Q. Dong, Y.N. Zhang, B. Cheng, Analysis of 8 cases of botulinum toxin A injection poisoning, *Chin J Ae Med* 32 (3) (2023) 59–61.
- [3] M. Pirazzini, O. Rossetto, R. Eleopra, C. Montecucco, Botulinum neurotoxins: biology, pharmacology, and toxicology, *Pharmacol. Rev.* 69 (2) (2017 Apr) 200–235, <https://doi.org/10.1124/pr.116.012658>.
- [4] J. Long, N. Jiang, Clinical characteristics and treatment of botulinum toxin type A poisoning by injection, *Chin J Med Beaut* 11 (4) (2021) 4, <https://doi.org/10.19593/j.issn.2095-0721.2021.04.001>.
- [5] Li Fang, C.L. Deng, One case of botulinum toxin poisoning, *Chin J Local Surg* (3) (2022) 31.
- [6] A. Rouientan, H. Alizadeh Otaghvar, H. Mahmoudvand, A. Tizmaghz, Rare complication of botox injection: a case report, *World J. Plast. Surg.* 8 (1) (2019 Jan) 116–119, <https://doi.org/10.29252/wjps.8.1.116>.
- [7] K.P. Bhatia, A. Münchau, P.D. Thompson, M. Houser, V.S. Chauhan, M. Hutchinson, A.H. Shapira, C.D. Marsden, Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases, *J. Neurol. Neurosurg. Psychiatry* 67 (1) (1999 Jul) 90–93, <https://doi.org/10.1136/jnnp.67.1.90>.
- [8] N. Thirunavukkarasu, E. Johnson, S. Pillai, D. Hodge, L. Stanker, T. Wentz, B. Singh, K. Venkateswaran, P. McNutt, M. Adler, E. Brown, T. Hammack, D. Burr, S. Sharma, Botulinum neurotoxin detection methods for public health response and surveillance, *Front. Bioeng. Biotechnol.* 6 (2018 Jun 22) 80, <https://doi.org/10.3389/fbioe.2018.00080>.
- [9] A.K. Rao, J. Sobel, K. Chatham-Stephens, C. Luquez, Clinical guidelines for diagnosis and treatment of botulism, 2021, *MMWR Recomm. Rep. (Morb. Mortal. Wkly. Rep.)* 70 (2) (2021 May 7) 1–30, <https://doi.org/10.15585/mmwr.rr7002a1>.
- [10] X.Q. Huang, Z.T. Ding, X.Y. Qiao, X. Chen, F.D. Liu, Iatrogenic botulism (a report of 3 cases and literature review), *Chin. J. Neurosci.* 25 (5) (2017) 4, <https://doi.org/10.3969/j.issn.1008-0678.2017.05.009>.
- [11] X. Zhao, H. Wang, Research status of diagnosis and treatment of botulism, *Disaster Med Rescue* (3) (2015) 3, doi: CNKI:SUN:ZAIY.0.2015-03-020.