

A Case of Acute Pulmonary Complication due to Botulinum Toxin: Patient with Central Pontine Myelinolysis Developed Acute Respiratory Distress Syndrome after Botulinum Neurotoxin Type A Injection Into Spastic Lower Extremity Muscles

Hasan Hüseyin Gökpınar¹ and Furkan Ertürk Urfalı¹

¹Kütahya Health Sciences University

April 3, 2023

Abstract

Purpose Chemodenervation with botulinum neurotoxin type A (BoNTA) is the preferred method for focal spasticity management among various treatment options. While BoNTA injection is considered safe, its widespread use and increasing evidence raise safety concerns. Case In this paper, we present a patient with central pontine myelinolysis, a rare disease, who developed Acute Respiratory Distress Syndrome (ARDS) on the third day after BoNTA application to the spastic gastrocnemius muscle group and required intubation in the intensive care unit due to this complication. Conclusion To our knowledge, this is the first case reported in the literature to develop an acute pulmonary complication after BoNTA injection into spastic lower extremity muscles.

Introduction

Central pontine myelinolysis (CPM) was first defined in 1959 as demyelination of the pons center due to osmotic imbalance in malnourished patients (1). It most commonly occurs due to hyponatremia and its rapid correction (2). Typically, CPM is clinically characterized by acute quadriparesis, dysphagia, and dysarthria. Cranial nerve involvement, ocular involvement, sensory changes, and mental impairment can also be seen. The most common and dramatic symptom is motor abnormalities.

Among various treatment options, chemodenervation with botulinum neurotoxin type A (BoNTA) is the preferred method for focal spasticity management (3). Over the last 30 years, accumulating evidence has proven the efficacy of BoNTA therapy (4,5), which usually starts on the second to third day of application, reaching the maximum level within three to four weeks and lasting for approximately three months (6). BoNTA injection is considered safe; however, its widespread use and increasing evidence raise safety concerns (7). Studies have reported local side effects due to BoNTA injection, such as pain at the injection site, edema, ecchymosis, hyperesthesia, and headache, which are generally well tolerated (8,9). Systemic side effects include nausea, weakness and fatigue, generalized weakness, dysphagia, respiratory distress, rash, and flu-like symptoms (9). Side effects vary according to the application and usually depend on the diffusion of the toxin from the muscle where the drug has been administered to the adjacent muscles (10). In our case, a systemic side effect was observed far from the local injection site.

In this paper, we present patient with CPM, a rare disease, who developed ARDS on the third day after BoNTA application to the spastic gastrocnemius muscle group-who did not have any past BoNTA interventions- and required intubation in the intensive care unit due to this complication. Our main purpose is to warn BoNTA practitioners about possible post-injection complications and to draw their attention to the possibility of such an acute and dramatic pulmonary involvement. To our knowledge, this is the first case

reported in the literature to develop an acute pulmonary complication after BoNTA injection into spastic lower extremity muscles.

Case

A 35-year-old female patient that developed CPM due to the rapid correction of hyponatremia in an external center was admitted to our hospital for neurorehabilitation and walking rehabilitation with robotics. The patient had a history of intensive care admission and a closed tracheostomy. At the time of admission to our hospital, she was spontaneously breathing without any problem except mild wheeze. The patient's vital signs were as follows: oxygen saturation stable at 98 mmHg, pulse 62/min, respiratory rate 18 breaths per minute, body temperature 36.5 °C, and arterial blood pressure 100/70 mmHg. She had moderate dysarthric speech and was using warfarin sodium due to atrial fibrillation. There was no abnormal finding in her blood values during hospitalization and follow-up. She was conscious, cooperative, and oriented. In the neurological examination, muscle strength was grade 1 for the right upper extremity proximal and lower extremity distal groups and grade 3-4 for the remaining key motor muscle groups according to Lovett Scale. Spasticity was grade 1+ for upper extremities, grade 2 for the lower extremity proximal group, grade 3 for the gastrocnemius group on the right, and grade 2 for the gastrocnemius group on the left according to Modified Ashworth Scale. Her ambulation level was stage 1 according to Functional Ambulation Classification (FAC) Scale. The patient was observed to have ambulation potential but her spasticity was more prominent than loss of muscle strength. Therefore, first, the INR level was reduced below 2 with the adjustment of the warfarin sodium dose, and then a total of 300 units of BoNTA injection were applied as follows: 50 units each into the four points of the medial and lateral heads of the right gastrocnemius muscle group and 50 units each into the two different points of the medial and lateral heads of the left gastrocnemius muscle group.

After the injection, the patient's general condition was good throughout the day and the next day, and she did not report any complaints. However, respiratory distress occurred on the third day of the injection. The patient's respiratory rate was 36/min, pulse 52/min, blood pressure 100/60 mmHg, and body temperature 36.5 degC. Despite the provision of high oxygen support, the SaO₂ value dropped from 97 mmHg to 92 and then 78 mmHg. The departments of chest diseases, anesthesia and reanimation, and cardiology were consulted immediately. The consultant cardiologist did not consider congestive heart failure in the patient since her ejection fraction was 55% on echocardiography. There were also no signs of congestive heart failure, such as right heart or hepatic vein dilatation, on the non-contrast thoracic computed tomography (CT) of the patient. Hypoxemia did not improve under 10 l/min O₂ support and arterial blood gas pH was compatible with acidosis; therefore, the patient was admitted to the intensive care unit and intubated. The non-contrast thoracic CT revealed bilateral parenchymal ground glass opacities accompanied by consolidation areas in the lower lobes. The patient was ventilated following the ARDS protocol and dual broad-spectrum antibiotherapy, IV methylprednisolone at 40 mg 1x1, bronchodilator nebulae, and IV acetylcysteine were started. In the intensive care follow-up, the patient's SaO₂ values improved but it was anticipated that she would have required mechanical ventilator support for a long time; thus, a tracheostomy was performed. During the follow-up, the patient's vitals remained stable. At the request of the patient relatives, the patient was transferred to a closer hospital in their city of residence.

Discussion

In this paper, we shared a case of acute pulmonary complication that resulted in the need for intensive care and intubation on the third day after treatment of focal spasticity with BoNTA in a patient with CPM. When we examined the literature in terms of BoNTA-related pulmonary complications, we found that Oliver et al. published clinical correspondence in 2018, in which they described a gradual decrease in pulmonary function over time, which returned to normal after BoNTA discontinuation during long-term treatment of migraine (11). We did not see any case in which pulmonary involvement developed in an acute dramatic manner as in our case. In addition, a multicenter study conducted in 2006 investigating the pulmonary effect of BoNTA reported that this treatment was safe without pulmonary complications (12).

It is known that after BoNTA applications, respiratory failure may develop due to paralysis of the respiratory

muscles, which may result in death. In our case, we initially considered the paralysis of the respiratory muscles since the patient worsened approximately 72 hours after the BoNTA injection. Pulmonary involvement was not expected at first, and it was thought that the respiratory muscles were likely to be affected by toxins and that a tracheostomy would probably be required. However, the presence of bilateral consolidation in the lungs and areas of infiltration of ground-glass opacity on the thoracic CT taken during the intensive care period further complicated the case by revealing that the situation was not actually expected based on our knowledge that systemic complications associated with BoNTA therapy were uncommon and such an acute pulmonary complication had never been encountered before. However, the radiological findings on thoracic CT being interpreted in favor of ARDS, clinical indications, and absence of any other condition that could explain the etiology supported the possibility of a BoNTA-related pulmonary complication.

In a study in which the intranasal administration of BoNTA-related pulmonary involvement was evaluated in mice, some histopathological changes were detected in the lungs despite the protection of the animals against neurotoxic effects. Although this situation was not considered to be direct toxin poisoning, it was suggested to have occurred with alveolar hemorrhage due to pulmonary capillary endothelial injury caused by a secondary cytokine-mediated inflammatory reaction triggered by the toxin, which led to the development of interstitial edema (13). Similarly, in two studies, Ermert et al. observed widespread endothelial weakening in the electron microscopic examination of the lungs of rabbits poisoned with botulinum toxin c2 and found edema formation due to increased permeability in pulmonary capillaries (14,15).

In the retrospective evaluation of our patient, the ground glass opacities observed in the thoracic CT scan, rapid improvement in her clinical state according to the laboratory findings, and increased pulmonary capillary permeability and endothelial damage due to BoNTA and other toxin types reported in animal experiments in the literature primarily suggested that our patient developed an acute pulmonary complication in which pulmonary edema was seen due to increased capillary permeability associated with BoNTA.

Conclusion

We consider that sudden respiratory distress and clinical ARDS signs in the current case went far beyond the involvement of respiratory muscle paralysis and suggested a pulmonary complication directly related to increased capillary permeability leading to ARDS as a result of BoNTA injection, a possibly fatal systemic adverse effect.

Conflict of interest statement: The authors declared no conflicts of interest with respect to the authorship and/or publication of this report. **Funding information:** This research did not receive any external funding and the authors did not receive any financial benefits.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement: As the present study is a single case report, patient's informed consent is obtained (please see included patient consent form). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Author contributions: Study conception and design: H.H.G., F.E.U.; Data collection and materials: H.H.G.; Literature review and control: H.H.G. ; Analysis and interpretation of results: H.H.G., F.E.U.; Writing the manuscript: H.H.G.

References

1. Adams RD, Victor M, Mancall EL: Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholic and malnourished patients. *MA Arch Neurol Psychiatr.* 1959; 81:154-72.
2. Singh TD, Fugate JE, Rabinstein AA: Central pontine and extrapontine myelinolysis: a systematic review. *Eur J Neurol .* 2014; 21:1443-50.
3. Simpson DM, Hallett M, Ashman EJ, et al: Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the

Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2016, 86, 1818–1826.

- Rosales RL, Chua-Yap, AS: Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J. Neural Transm.* 2008, 115, 617–623.
- Andringa A, van de Port I, van Wegen E, et al: Effectiveness of botulinum toxin treatment for upper limb spasticity after stroke over different ICF domains: A systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* 2019, 100, 1703–1725.
- Francisco GE, Li S. Spasticity. In *Braddom’s Physical Medicine and Rehabilitation* , 5th ed.; Elsevier: Philadelphia, PA, USA, 2015.
- Sethi N, Singh S, DeBouille K, et al: A Review of Complications Due to the Use of Botulinum Toxin A for Cosmetic Indications. *Aesth Plast Surg* 2020; Published online, <https://doi.org/10.1007/s00266-020-01983-w>
- Ramirez-Castaneda J, Jankovic J: Long-term efficacy and safety of botulinum toxin injections in dystonia. *Toxins*(Basel)2013;5(2):249–66.
- Baizabal-Carvalho JF, Jankovic J, Pappert E: Flu-like symptoms following botulinum toxin therapy. *Toxicon* 2011;58(1):1–7.
- Moore AP: Movement, visceral and autonomic disorders: use of botulinum toxin. *Hospital Med* 2003;64:452–9.
- Oliver, JD, Boesch RP, Mack KJ: Decreased Pulmonary Function During Botulinum Toxin A Therapy for Chronic Migraines in a 17-Year-Old Female. *Headache: The Journal of Head and Face Pain*2018;58(8), 1259-1261.
- Schoene R, Brashear A, Turkel CC, et al: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Multicenter Study Evaluating the Effect of Botulinum Toxin Type A Treatment on Pulmonary Function in Patients With Poststroke Focal Spasticity. *Archives of Physical Medicine and Rehabilitation* 2006; 87(11), e10.
- Taysse L, Daulon S, Calvet JH, et al: Induction of acute lung injury after intranasal administration of toxin botulinum a complex. *Toxicologic pathology* 2005;33 (3), 336-342.
- Ermert LE, Bruckner HE, Walmrath DI, et al: Role of endothelial cytoskeleton in high-permeability edema due to botulinum C2 toxin in perfused rabbit lungs. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 1995, 268.5: L753-L761.
- Ermert L, Duncker HR, Bruckner H, et al: Ultrastructural changes of lung capillary endothelium in response to botulinum C2 toxin. *Journal of Applied Physiology* 1997, 82.2: 382-388.

Table 1: Patient’s laboratory findings over time and important dates

Figure 1: Non-contrast thoracic CT image in the axial plane, revealing bilateral ground glass opacities in upper lobe sections (a) and consolidation areas in lower lobe sections (b)

Figure 2: Non-contrast thoracic CT image in the coronal plane, showing diffuse ground glass opacities in both lungs

Supplemental Digital Content

CARE Checklist

Patient Consent Form

1. Consent Form

Hosted file

table 1.docx available at <https://authorea.com/users/602369/articles/633253-a-case-of-acute-pulmonary-complication-due-to-botulinum-toxin-patient-with-central-pontine-myelinolysis-developed-acute-respiratory-distress-syndrome-after-botulinum-neurotoxin-type-a-injection-into-spastic-lower-extremity-muscles>



