Acta Scientific PAEDIATRICS (ISSN: 2581-883X)

Volume 5 Issue 4 April 2022

Case Report

Botulinum Toxin A (Btx-A) Injection: A Rare and Complicated Pediatric Case from Kurdistan, Iraq

Nizar Bakir Yahya[1], Hevan Adel Al-Atroushy[2], Stefano Maiandi[3] and Federica Buzzi[4]*

[1]MBChB, FIBMS and Assistant Professor, College of Medicine, Department of Pediatric, University of Duhok, Duhok, Iraq

[2]Pediatrician FIBMS, Pediatric Intensive Care Unit, Hevi Pediatric Teaching Hospital Duhok, KR, Iraq

[3]MsN, Professional Development and Research, Directorate of Health Professions, ASST of Lodi

[4]RN, Head of pediatric and neonatal intensive care clinical training, E.U. Project MADAD, Italian Association for Solidarity among Peoples, Duhok, KR, Iraq

Nurse, Hematology and Bone Marrow Transplantation Unit and Pediatric Immunohematology Unit, IRCCS San Raffaele Scientific Institute, Milan

***Corresponding Author:** Federica Buzzi, RN, Head of pediatric and neonatal intensive care clinical training, E.U. Project MADAD, Italian Association for Solidarity among Peoples, Duhok, KR, Iraq.

DOI: 10.31080/ASPE.2022.05.0511

Received: December 13, 2021

Published: March 25, 2022

Abstract

Botulinum neurotoxin is the most potent poison known to humans. The active form of the Clostridium botulinum spore produces a neurotoxin that causes paralysis. Many botulism presentations are subtle and difficult to diagnose. However, botulinum can also have therapeutic uses, and the indications are different, including the reduction of muscle spasticity in pediatric patients. The therapeutic use of botulinum toxin can cause several complications, including the possibility of developing botulism.

Treatment of botulism consists of administration of antitoxins, hospitalization, close monitoring, and respiratory support as needed. The mortality rate of patients who develop botulism has dramatically decreased in developing countries but not in low-middle income countries because resources are severely limited. We report the first case of botulism after botulinum injection in a patient with hypoxic ischemic encephalopathy. The diagnosis was very complicated and late given the scarce resources present in Kurdistan, Iraq. The patient required advanced and long-lasting care.

The child was hospitalized for 92 days, 56 of which the patient was on mechanical ventilation. The patient was treated without any antidote as it was not present, and he had no further neurological sequelae following the event.

Keywords: Botulinum Toxin; Injection; Pediatric; Complicated

Abbreviations

BIG-IV: Botulism Immune Globulin Intravenous (Human); BTX-A: Botulinum Toxin A; CBC: Complete Blood Count; CRP: C-Reactive Protein; CSF: Cerebrospinal Fluid; HFNC: High Flow Nasal Cannula; HIE: Hypoxic Ischemic Encephalopathy; P-GCS: Pediatric Glasgow Coma Scale; PICU: Pediatric Intensive Care Unit; WBCs: White Blood Cells

Introduction

Botulinum neurotoxins are the most powerful biological toxins known in the natural world; for this reason, botulism is a dangerous but, above all, rare disease that can affect individuals of all ages [1,2] Botulism is caused by the production of a powerful botulinum toxin by the bacterial spore *Clostridium botulinum*. Several presentations of foodborne, inhalation, neonatal, wound, and intestinal

colonization of adults and iatrogenic botulism have been described [3,4] The most common human botulism form is infantile, while all other presentations are rare [5]. Botulinum neurotoxin is transported through the bloodstream to the presynaptic terminal of motor neurons [6]. Neurotoxins act on the neuromuscular junction, causing dose-dependent muscle paralysis by inhibiting the release of acetylcholine from presynaptic motor neurons [7] The botulinum toxins produced will irreversibly bind to peripheral motor nerve terminals and enter motor neurons, where they inhibit the release of acetylcholine. This inhibition results in the characteristic descending and symmetrical flaccid paralysis [8] The classic presentation of symmetrical descending paralysis is often initially absent in young children with the disease and is often replaced by an ill-defined major disorder, which includes poor nutrition and lethargy [9] Therapeutic contexts for botulinum toxin injection are focal dystonia, spasticity, nondystonic disorders of involuntary muscle activity, strabismus, chronic pain and localized muscle spasm disorders, overactive smooth muscle disorders, cosmetics, salivary sweating, and allergic disorders [10] Since 1993, intramuscular injections of Botulinum Toxin A (BTX-A) have been used to reduce spasticity in individuals with cerebral palsy and, more generally, in children with spasticity due to other causes, such as hypoxic ischemic encephalopathy (HIE). BTX-A reduces spasticity and maintains a favorable range of motion to prevent vicious joint patterns [11,12] However, despite its established safety, postinjection adverse effects may occur very rarely and are sometimes responsible for systemic toxicity due to the spread of the toxin beyond the injection site [13] Symptoms appear within 5 to 10 days after the injection of BTX-A [14] and initial manifestations include bilateral ptosis, dysphagia, dysarthria, and upper and lower limb weakness, as predicted by the typical descending paralysis characteristic of botulism [15]

Case Description

A 3-year-old male born premature and known to have HIE was admitted to the emergency room of the Hevi Pediatric Teaching Hospital in Duhok, Iraq, after three days of fever, fatigue, weakness of the left side of the body and loss of appetite. The patient's vital signs were as follows: temperature of 38.0°C; heart rate of 178 beats/min; respiratory rate of 24 breaths/min; blood pressure of 100/60 mmHg; and 97% oxygen saturation in ambient air. On physical examination, the patient was alert, with a Pediatric Glasgow Coma Scale (P-GCS) of 14. Neurological examination revealed diffusely decreased tone with weak deep tendon reflexes, and the muscle power scale score was 3. The complete blood count (CBC) showed an increase in white blood cells (WBCs) and platelets. Electrolytes and liver and kidney function were normal, and the C-reactive protein (CRP) level was high. The cerebrospinal fluid (CSF) evaluation was normal, and the cultures were negative. Three days after admission, the patient was hypotonic and hyporeactive, and for this reason, he was admitted to the semi-intensive care unit. A high-flow nasal cannula (HFNC) was necessary to decrease his oxygen saturation (85% on room air). The possible initial diagnoses were related to sepsis, dehydration and encephalopathy. After 2 weeks of admission, the patient presented with an episode of apnea requiring endotracheal intubation and was transferred to the pediatric intensive care unit (PICU) to initiate mechanical ventilation. The child's neurological condition continued to deteriorate deep tendon reflexes became diffusely absent, the pupils responded slowly to light, and the child had no significant spontaneous movement, with a muscle power scale score of 0. After a more thorough medical history was retrieved by the caregiver, it was learned that the child had received an injection of BTX-A by prescription from the primary care physician as a cure for the patient's HIE. The injections were performed 6 days before admission (100 IU in the right posterior thigh muscle and 100 IU in the left posterior thigh), and several injections were administered in different parts of the muscle. The diagnosis of botulism was made on the basis of the patient's medical history and symptoms. Meropenem, vancomycin and acyclovir were administered intravenously for 15 days. The continued need for mechanical ventilation and the lack of significant clinical improvement resulted in the patient having two cardiac arrests. Pyridostigmine therapy was initiated (supplemental material), after which the patient began to experience significant clinical improvement. The child was able to be extubated on day 56 of admission to the ICU and discharged 92 days after presentation. The child has been followed for 6 months and has had no major persistent consequences; he had a known slightly decreased left-side body muscle tone from his existing HIE, with a muscle power scale score of 4.

Discussion

This is the first reported case of botulism related to botulinum toxin A (BTX-A) injection in the autonomous region of Kurdistan, Iraq. Furthermore, this is the first reported case of systemic botulism in a patient with HIE [16] This case illustrates the importance of promptly considering the diagnosis by obtaining a thorough medical history and a thorough clinical examination of the patient.

Injecting BTX-A into the upper limb to improve posture and motor function in patients may be one of the therapies used for children with HIE, but this can lead to the rare complication of botulism [17]

Classically, symptoms of botulism include symmetrical descending paralysis, which begins with cranial nerve palsy manifested as ptosis, slow pupillary reflex, and loss of the gag reflex and eventually leads to loss of deep tendon reflexes and respiratory failure

over the course of hours or days [18] The toxin produces local paralysis by blocking the presynaptic release of the neurotransmitter acetylcholine in the neuromuscular junction and thus reduces hyperactivity and spasticity in the muscle [19-21] For this reason, the patient was evaluated with the muscle power scale to understand the capacity of his muscle, which ranged from four to zero, during its maximum criticality. The diagnosis of botulism is based on clinical suspicion, and it can be confirmed by identifying the BOTX-A in the patient's stool or serum or by isolating the toxin-producing BTX-A clostridia in the patient's stool samples. Neither of these options was possible for the patient described in our report, as the tests are not available in all Kurdish territories. Treatment indications are largely based on clinical experience, and there is a lack of established guidelines for the treatment procedure [22].

With early diagnosis and advanced intensive care, children with botulism have very low mortality in developed countries. The most serious complication of botulism is respiratory failure requiring ventilation support, which is required in over 70% of cases. The management of children with botulism revolves around meticulous supportive care, the use of human anti-botulin immunoglobulins, and careful selection of antibiotics. Botulism Immune Globulin Intravenous (BIG-IV) works to neutralize free botulinum toxin; however, it does not immediately improve symptoms. It further prevents toxin binding, resulting in faster clinical improvement [23-26] The patient described in our clinical case was unable to receive BIG-IV, as it is not available throughout Iraq. In addition, particular attention must be paid to the selection of antibiotics for patients with this potential botulism, as particular classes of drugs, such as aminoglycosides, can cause further release of toxins or further prevent the release of acetylcholine [27] As such, managing a botulism patient in a middle-income country is very difficult and complicated due to the limited resources available to healthcare professionals [28] Given the impossibility of using BIG-IV, the use of pyridostigmine was considered for our patient. Pyridostigmine, an acetylcholinesterase inhibitor, prevents the degradation of acetylcholine at the neuromuscular junction. This could explain the child's initial improvement without the administration of antitoxins. Pyridostigmine may play a role in reducing disease severity as an adjunct therapy in the management of botulism [29].

Conclusion

The neurological recovery of this patient in the hospital was very long and complicated with a prolonged period of assisted mechanical ventilation in the PICU and a hospital stay. For children who require mechanical ventilation, the average duration is 23 days [30] The average hospital stay is 44 days. In general, neurological sequelae are rare. Persistent hypotonia may be present upon discharge from the hospital, but recovery is complete and can be expected with time [31].

Bibliography

1. Jankovic J and Brin MF. "Botulinum toxin: historical perspective and potential new indications". *Muscle Nerve Supply* 6 (1997): S129-145.

2. Jankovic J. "An update on new and unique uses of botulinum toxin in movement disorders". *Toxicon* 147 (2018): 84-88.

3. Anniballi F., *et al*. "New targets in the search for preventive and therapeutic agents for botulism". *Expert Review of Anti-infective Therapy* 12.9 (2014): 1075-1086.

4. Anniballi F., *et al*. "Foodborne botulism associated with home-preserved turnip tops in Italy". *Annali dell'Istituto Superiore di Sanità* 51.1 (2015): 60-61.

5. Wilkes J. "AAN Updates Guidelines on the Uses of Botulinum Neurotoxin". *American Family Physician* 95.3 (2017): 198-199.

6. Sobel J and Rao AK. "Making the Best of the Evidence: Toward National Clinical Guidelines for Botulism". *Clinical Infectious Diseases* 66.1 (2017): S1-S3.

7. Martin S-J., *et al*. "Wound botulism, its neurological manifestations, treatment and outcomes: A case series from the Glasgow outbreak, 2015". *Scottish Medical Journal* 62.4 (2017): 136-141.

8. Opila T., *et al*. "Trends in Outcomes and Hospitalization Charges of Infant Botulism in the United States: A Comparative Analysis Between Kids' Inpatient Database and National Inpatient Sample". *Pediatric Neurology* 67 (2017): 53-58.

9. Griese SE., *et al*. "Pediatric Botulism and Use of Equine Botulinum Antitoxin in Children: A Systematic Review". *Clinical Infectious Diseases* 66.1 (2017): S17-S29.

10. Szuch E., *et al*. "Head drop after botox: Electrodiagnostic evaluation of iatrogenic botulinum toxicity". *Clinical Neurology and Neurosurgery* 156 (2017): 1-3.

11. Koman LA., *et al*. "Management of cerebral palsy with botulinum-A toxin: preliminary investigation". *Journal of Pediatric Orthopaedics* 13.4 489-495.

12. Novak I., *et al*. "State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy". *Current Neurology and Neuroscience Reports* 20.2 (2020): 3.

13. Strobl W., *et al*. "Best Clinical Practice in Botulinum Toxin Treatment for Children with Cerebral Palsy". *Toxins (Basel)* 7.5 (2015): 1629-1648.

14. Nahm NJ., *et al*. "Management of hypertonia in cerebral palsy". *Current Opinion in Pediatrics* 30.1 (2018): 57-64.

15. Chatham-Stephens K., *et al*. "Clinical Features of Foodborne and Wound Botulism: A Systematic Review of the Literature, 1932-2015". *Clinical Infectious Diseases* 66.1 (2017): S11-S16.

16. Murray DM., *et al*. "Early EEG Grade and Outcome at 5 Years After Mild Neonatal Hypoxic Ischemic Encephalopathy". *Pediatrics* 138.4 (2016).

17. Jankovic J. "Botulinum toxin: State of the art". *Movement Disorders* 32.8 (2017): 1131-1138.

18. Fortunato F., *et al*. "Food-borne botulism in Apulia region, Italy: an expert witness testimony". *Ann Ig* 31.2 181-185.

19. Kuehn B. "Wound Botulism Outbreak". *JAMA* 321.6 (2019): 538.

20. Kumar R., *et al*. "The Botulinum Toxin as a Therapeutic Agent: Molecular Structure and Mechanism of Action in Motor and Sensory Systems". *Seminars in Neurology* 36.1 (2016): 10-19.

21. Ibatullin RA and Magjanov RV. "Case of iatrogenic botulism after botulinotherapy in clinical practice". *Terapevticheskii arkhiv* 90.11 (2018): 102-104.

22. Hollung SJ., *et al*. "Completeness and correctness of cerebral palsy diagnoses in two health registers: implications for estimating prevalence". *Developmental Medicine and Child Neurology* 59.4 (20177): 402-406.

23. Arnon SS., *et al*. "Human botulism immune globulin for the treatment of infant botulism". *The New England Journal of Medicine* 354.5 (2006): 462-471.

24. Yu PA., *et al*. "Safety and Improved Clinical Outcomes in Patients Treated With New Equine-Derived Heptavalent Botulinum Antitoxin". *Clinical Infectious Diseases* 66.1 (2017): S57-S64.

25. Richardson JS., *et al*. "Safety and Clinical Outcomes of an Equine-derived Heptavalent Botulinum Antitoxin Treatment for Confirmed or Suspected Botulism in the United States". *Clinical Infectious Diseases* 70.9 (2020): 1950-1957.

26. Toubiana J., *et al*. "Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study". *BMJ* 369 (2020): m2094.

27. Chalk CH., *et al*. "Medical treatment for botulism". *Cochrane Database of Systematic Reviews* 4 (2019): CD008123.

28. Carrillo-Marquez MA. "Botulism". *Pediatric Review* 37.5 (2016): 183-192.

29. Boerner RM., *et al*. "Pyridostigmine for the Reversal of Severe Adverse Reactions to Botulinum Toxin in Children". *Journal of Pediatrics* 194 (2018): 241-243.

30. Pirazzini M and Rossetto O. "Challenges in searching for therapeutics against Botulinum Neurotoxins". *Expert Opinion on Drug Discovery* 12.5 (2017): 497-510.

31. Walsh K. "Case reports on dangerous infectious diseases: a review of patient consent". *BMJ Military Health* 166.3 (2020): 179-180.