Outbreak of foodborne botulism in Alexandria, Egypt: modulating indications for administration of heptavalent botulinum antitoxin

Sara A. Ghitani 1 · Maha A. Ghanem 1 · Eman A. Sultan 2 · Maram Atef 1 · Maii F. Henaidy 1

Received: 11 March 2021 / Accepted: 10 June 2021 / Published online: 28 June 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract
In October 2019, ninety-four patients were admitted into Alexandria Poison Center (APC) with a history of ingestion of Feseekh (salted fish). In an attempt to allocate the resources, not all patients were given HBAT (botulism antitoxin heptavalent (A, B, C, D, E, F, G) equine immediately. The current study aimed to portray the clinical characteristics of the cases, explore the possible relation between these characteristics and necessity of HBAT administration, explore the reliability of mouse lethal test, and establish a clinical guide for management including preservation of resources. The current prospective study included 94 patients who were admitted to Alexandria Poison Center (APC) in the period from the 29th of September to the 27th of October 2019. The patients’ data were recorded using a checklist that includes: personal data, past medical history, clinical assessment, investigations, treatment, and the outcome. The checklist was carried out to assess and follow up each patient. Hospitalized patients were categorized according to symptoms consistent with botulism. The equine HBAT, made by Emergent BioSolutions Canada Inc. (formerly Cangene Corporation), was used in the treatment. HBAT was given to thirty-four patients (36.2%) only out of the total admission. However, eighty-two (87.2%) of patients were completely cured, whereas ten patients (10.6%) were discharged with mild neurological sequels and death occurred only in two cases (2.2%). Sixty cases (63.8%) with suspected foodborne botulism could be managed by supportive treatment only with no need for HBAT, while patients with evident neurological signs received HBAT immediately.

Keywords Botulism · Heptavalent botulinum antitoxin · Outbreak

Introduction
Botulism is considered one of the recurrent events that challenge poison centers, in Egypt, each year due to a traditional salted fish meal which is consumed each spring Weber et al. (1993). In the spring (April) of 2019, there were fifty-eight cases of suspected botulism admitted to APC and only three cases needed the botulinum antitoxin. However, they suffered from side effects including severe epistaxis and one case arrested during anti-toxin administration. On the 29th of September 2019, a child was transferred to APC for differential diagnosis of paralytic ileus as her family said she was given a piece of salted fish (feseekh) and she was considered the first case of the outbreak. The preliminary assessment of the situation was carried out and preparations were made to confront a large outbreak out of season.

A collaborative team from APC doctors with the Egyptian Ministry of Health (EMOH) was initiated to conduct interviews with the cases investigating the source, the onset time of the symptoms, other members of the family exposed to the
same meal, etc. Blood specimens were collected from the cases. Factors common to all cases were identified and formulated preliminary hypotheses were issued. The team delivered a daily report to the authorities, and all types of media were used to issue a warning until the outbreak was stopped on the 27th of October 2019. The Egyptian news declared previously the death of almost 100 tons of “mullet” fish and veterinarians warning of the mass death of fish in a small town called Rashid which was considered the source of that outbreak. Veterinarians warn of the mass death of fish in Lake Rashid (2019).

Due to delay in results of mouse lethal test (MLT) and the false-negative results due to low levels of toxin in the serum or delayed diagnosis, the APC team treated the cases depending on the clinical picture (Lindstrom and Korkeala 2006, Chaudhry 2011, Wilder-Kofie et al. 2011, Wheeler et al. 2009). We tried to decrease the exposure of the patients to the side effects of the antitoxin due to our unpleasant experience with heptavalent botulinum antitoxin in the spring of the same year (Richardson et al. 2020).

The current study aimed to portray the clinical characteristics of the cases, to explore the possible relation between these characteristics and necessity of HBAT administration, to explore the reliability of MLT, and to establish a clinical guide of management of the suspected cases of botulism with preservation of resources.

Subjects and methods

I. Research strategy and design: The descriptive epidemiological approach was selected.

II. Research setting:

1. Target population and place: All patients admitted to APC—the main university hospital—with a history of salted fish (Feseekh) ingestion during the outbreak (94 cases)
2. Time: from 29 September to 27 October 2019
3. Ethical consideration: The approval of the Ethical Committee of the Faculty of Medicine for the present study was obtained.

III. Research tools:

A checklist and record review were carried out for the collection of data to assess and follow up each patient. The equine heptavalent botulism antitoxin (A, B, C, D, E, F, G), made by Emergent BioSolutions Canada Inc. (formerly Cangene Corporation), was used in treatment.

Mouse bioassay for clostridium botulinum toxin was performed following FDA’s Bacteriological Analytical Manual. The blood samples were taken on the arrival of the patient to the poison center, centrifuged, and sent directly to the laboratory on transfer sample bags. The test was conducted in the central public health laboratories (CPHL) which are accredited according to ISO 17025 for testing labs and 15189 for clinical labs.

IV. Categorization of patients:

Clinical assessment was completed for all cases and a checklist including different signs and symptoms of botulinum toxicity was fulfilled on admission.

To properly manage the resources, the patients were classified into groups according to their clinical assessment that was repeated every 1 h. If the signs and symptoms were improving, assessment follow-up would be every 6 h.

The patients’ groups were as the following:

Group A included those with a history of Feseekh ingestion and who were completely normal on their first assessment and throughout their hospital stay (3 cases). They sought medical advice as they ate feseekh with other family members who presented with botulinum toxicity and were admitted under observation.

Group B included patients complaining of typical gastroenteritis throughout their course, i.e., nausea, vomiting, diarrhea, abdominal pain, and mild abdominal distention (38 cases). They received supportive treatment, e.g., fluids, antiemetic, antispasmodic, and were put under close observation and monitoring.

Group C included all cases who developed neurological or autonomic dysfunction symptoms whether GIT symptoms were present or not. They were further subdivided into two groups:

1. Group C1: those at the time of admission presented with evident serious neuromuscular dysfunction signs as ptosis, peripheral muscle weakness, or hypoventilation (20 cases). This group received the antitoxin immediately.
2. Group C2: those at time of admission presented with mild autonomic dysfunction as a dilated fixed pupil and/or blurring of vision, dry mouth and/or mild dysphagia, mild dysphonia and patients complained of constipation and/or severe abdominal distention and they received supportive treatment according to the complaint in the form of IV fluids, vitamin B12, and laxatives with close observation and monitoring. They were further classified according to their disease course into the following:

   • Patients with a progressive course whose signs increased in severity or who developed evident neuromuscular dysfunction signs or any other autonomic
dysfunction within 24 hours of observation, so they received the antitoxin immediately after the appearance of neuromuscular dysfunction (14 cases).

- Patients with stationary course who did not develop any additional neuromuscular paralysis signs during their period of observation, so they continued to receive supportive treatment only (19 cases).

V. Statistical methods:

The data were collected and stored in a computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software. Data was presented as numbers and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. For testing associations between qualitative variables, the chi-square test was used. The significance of the obtained results was judged at the 5% level.

Results

1. Demographic data

The highest percentage of the cases (42.6%) were in the age group 20 ≤ 40 years. This was followed in a descending manner by the age group <20 years (34%), then the age group of 40 ≤ 60 years (21.3%) and the age group ≥ 60 years (2.1%). More than two-thirds (69.1%) were females while 30.9% were males. As regard residence, 36.2% of the cases were from Alexandria, 35.1% came from Kafr El-Sheikh, 27.6% were from Elbehira, and only one case (1.1%) was living in Al-Ismailia.

2. Past medical history

In the current study, medical history of previous diseases, injuries, and operative procedures were taken from all participants. However, most of the studied patients (91.5%) had no history of chronic diseases.

3. History of salted fish (Feseekh) ingestion

All the participated cases presented to the hospital from 6 h to 9 days after Feseekh ingestion with a mean value of 1.70 ± 1.49 days.

4. Assessment of the cases

The most common findings observed in admitted patients were nausea and vomiting (76.6%), abdominal distension (41.5%), and dilated fixed pupil (29.8%) (Table 1).

5. Administration of HBAT

Thirty-four patients (36.2%) with serious evident neurological signs either at the time of admission or during observation received HBAT immediately. The first dose of HBAT was given through 0.33–6 days from Feseekh intake. Among those who received the first dose of HBAT, more than half (55.9%) of the cases improved completely. On the other hand, six patients (17.7%) showed no improvement with persistent symptoms and 9 cases (26.4%) showed temporary improvement followed by relapse. Those fifteen patients were given the second vial of the botulinum antitoxin. The time interval between the first and second vials was 1–4 days with a mean of 2.03± 0.93 days. Only one patient needed a third vial of the botulinum antitoxin. This was attributed to the persistence of hypoventilation one day after the second dose.

The patients in group C2 were further categorized according to the number of mild autonomic dysfunction complaints and the need for HBAT administration and the results revealed that:

All patients who were admitted to the hospital complaining of only one symptom of autonomic dysfunction did not need the antitoxin, while 100% of patients presented with four

| Clinical assessment | No. | % |
|---------------------|-----|---|
| Ocular              |     |   |
| Blurred vision      | 14  | 14.9 |
| Ptosis              | 11  | 11.7 |
| Mydriasis           | 28  | 29.8 |
| Bucco-pharyngeal    |     |   |
| Dry mouth           | 14  | 14.9 |
| Dysphagia           | 23  | 24.5 |
| Dysphonia           | 3   | 3.2  |
| Digestive           |     |   |
| Abdominal pain      | 7   | 7.4  |
| Constipation        | 24  | 25.5 |
| Distention          | 39  | 41.5 |
| Diarrhea            | 13  | 13.8 |
| Nausea and vomiting | 72  | 76.6 |
| Muscle weakness     | 20  | 21.3 |
| Grade               |     |   |
| II                  | 2   | 2.1  |
| III                 | 1   | 1.1  |
| IV                  | 17  | 18.1 |
| Respiratory         |     |   |
| Dyspnea             | 12  | 12.7 |
| Gasping             | 1   | 1.1  |
| Respiratory distress| 1   | 1.1  |

61549
autonomic symptoms needed the antitoxin during their period of observation. On the other hand, 77.8% of those with three autonomic dysfunction symptoms needed the antitoxin. However, half of those with only two autonomic symptoms developed neurological signs later and needed the antitoxin. And this difference is statistically significant with \( p < 0.001 \) (Table 2).

As regards the side effects of HBAT that appeared after administration in the current study, seven patients (20.5%) developed side effects; five of them developed epistaxis, one patient developed severe hypotension, and one patient developed severe numbness.

6. Result of mouse bioassay test

A blood sample was withdrawn from patients on admission to the poison center. It ranged from 6 h to 9 days after ingestion of the Feseekh and serum was prepared and transferred to the lab. Mouse bioassay test was carried out to 82 out of 94 cases and 87.8% was negative. It means that 24 cases with negative mouse bioassay test developed neurological symptoms and needed HBAT (Table 3).

7. Duration of hospitalization, ICU admission, and need for mechanical ventilation support

The duration of hospital admission was 1–12 days with a mean of 3.71 ± 2.75 days. Moreover, 30 patients (31.9%) admitted to ICU for a period ranged from 1 to 8 days with a mean of 3.40 ± 1.81 days. Eight patients (40%) from group C1 needed mechanical ventilation for a period of 1–5 days with a mean of 2.50 ±1.60 days.

8. The outcome

Recovery was the major outcome (87.2%) whereas neurological sequelae were present in 10.6% of patients—in the form of persistent constipation, distention, dry mouth with a very mild dysphagia, and death that occurred only in two cases (2.2%).

**Discussion**

On spring, Egyptians’ celebration of the eastern festival is accompanied with eating Feseekh (salted fish). The Egyptian Ministry of Health prepared for that situation at that time by importing HBAT bottles and sending them to all poison centers in Egypt during springtime for free. So antitoxin was previously given, as soon as possible, after the appearance of any mild anticholinergic complaints and even after consuming suspected food contaminated with botulinum toxin. However, an unexpected outbreak occurred in autumn, and it was justified by contamination of marine mullet meat during that time, where some of those contaminated fish were taken by some individuals and salted in their homes (Veterinarians warn of the mass death of fish in Lake Rashid 2019). Due to this out-of-season outbreak, with many cases that even exceeded the available HBAT, a modification for the management plan and the indications of HBAT was absolutely needed.

---

**Table 2** Relation between mild cranial deficit signs and administration of anti-toxin (n = 33)

| Number of mild cranial deficit signs | Anti-toxin      | Total | Statistical significance |
|-------------------------------------|-----------------|-------|--------------------------|
|                                     | Yes            | No    |                          |
| 1                                   | 0 (0.0%)       | 14 (100.0%) | 14 | \( p^{MC} = < 0.001^* \) |
| 2                                   | 3 (50.0%)      | 3 (50.0%)   | 6 |
| 3                                   | 7 (77.8%)      | 2 (22.2%)   | 9 |
| 4                                   | 4(100.0%)      | 0 (0.0%)    | 4 |
| Total                               | 14 (42.4%)     | 19 (57.6%)  | 33 |

*Minor cranial deficit signs include:
  - Dilated fixed pupil and/or blurred vision
  - Mild dysphagia and/or dry mouth
  - Mild dysphonia
  - Constipation and/or abdominal distension
  - Feeling of dyspnea without any signs of respiratory distress
The outbreak started with a 1.5-year-old child referred from the Pediatric University Hospital to APC for differential diagnosis. She presented with paralytic ileus that raised the suspicion of intussusception and surgical abdomen. On examination, the surgical emergency was eliminated. A similar scenario was mentioned by Spini et al. (2015).

Due to the unusually young age of the child with the absence of the common paralytic manifestations of botulism, pediatricians doubted botulism. Pisanti et al. (2009) had explained a similar situation as the initial symptoms of the disease are often like several diseases and therefore, differential diagnosis is very difficult and rarely suspected by the pediatrician.

Although the highest percentage of the patients were in the middle age group (20 ≤ 40 years), extremes of age were also involved, and females outnumbered males. This could be explained by the Egyptian culture where the ladies prepared the meals for the families as well as tasting them before meals. All family members gathered for celebration and ate the same food so different ages are usually affected.

APC is serving Alexandria and all-around governorates (Elbehira, Kafr el-Sheikh, Marsa Matrouh, etc.). As the accident of contamination of the mullet fish meat occurred in Elbehira governorate, so all patients were directed to APC as in all other poisons.

In the current work, 91.5% of the cases had no previous medical or surgical history. Past medical and surgical history was taken to exclude neurological diseases, previous stroke, and other gastrointestinal problems. All patient’s symptoms started to appear after eating the Feseekh meal. All the participated cases presented to the hospital from 6 h up to 9 days after Feseekh ingestion with a mean of 1.70 ± 1.49 days. In their systematic review, Fleck-Derderian et al. (2017) reported a median duration between exposure and symptom onset as approximately 1 day. This difference is expected due to the long incubation period of foodborne botulism which would reach up to 16 days.

The mouse lethal test (MLT) is the standard procedure for the detection of botulism. Mouse bioassay test was carried out in 82 out of 94 cases. The results delivered several days after the clinical diagnosis revealed that 87.8% of cases were negative despite the presence of clinical neurological manifestations. These negative results could be explained by the long period between the Feseekh ingestion and the withdrawal of serum samples as the samples were obtained from patients at the time of admission and many patients admitted to the hospital few days after the appearance of symptoms. Timing and nature of sample collection, ingested toxin dosage, kinetics of toxin absorption into the bloodstream, and uptake of toxin by the extravascular compartment are all factors that contribute to false-negative findings in human patients (Sobel 2009). This result is in accordance with that of Temeri et al. (2011) who stated that many clinical specimens have low levels of toxin which may not be evident within 4 days.

Although the clinical syndrome of botulism is distinctive, it needs a high index of suspicion to be diagnosed. In the current study, patients were presented with mydriasis (29.8%), blurred vision (14.9%), ptosis (11.7%), dysphagia (24.5%), and muscle weakness in 21.3% of patients. This is in accordance with Gaware et al. 2011 who reported these symptoms as the classic for botulism.

On contrary to most of the previous studies on Botulism that recommend early antitoxin administration to reduce mortality (Gaware et al. (2011), Kongsaengdao et al. (2006) and Yu (2015)), the current study aimed to manage the resources and to decrease the exposure of the patients to the side effects of the unnecessary administration of antitoxin. Thus, the patients in the current study were classified at the time of admission into three groups. Only twenty patients—group C1—who presented with severe evident neurological symptoms; ptosis, muscle weakness, or respiratory muscle paralysis with hypventilation were given the BAT immediately. While the rest of the patients did not receive the BAT immediately, they were put under close observation.

Patients in group A who presented to the hospital with just a history of Feseekh ingestion as members of their family ate the same meal and developed botulism manifestations and also patients in group B who presented with only gastrointestinal problems developed any additional symptoms during their period of hospitalization and did not need to receive the BAT. Moreover, patients in group C2 who presented with mild autonomic dysfunction did not receive the BAT immediately as most of the autonomic dysfunction complain of patients in group C2 might be just a subjective feeling due to the fear or anxiety that result from the warnings spread at that time on the media or due to their affection by other patients in the outbreak.

However, in order to identify patients likeliest to benefit from the antitoxin treatment, patients in group C2 were categorized according to the number of cranial deficit signs on initial assessment to anticipate the deterioration and to predict who would need the antitoxin administration which may be valuable for further development of guidelines. The initial assessment of cases with suspected food-borne botulism is very important.

In our opinion, this classification reduced the unnecessary administration of the HBAT to 60 patients who were managed by supportive treatment only. This protocol helped avoidance of many side effects of the antitoxin including the most severe ones as anaphylaxis and hypersensitivity reactions and other delayed allergic reactions as serum sickness. Schussler et al. (2017) reported anaphylactic reactions in 1–2% of botulinum antitoxin recipients that would be severe enough and necessitate intensive care.
Also, this is very important for prioritizing antitoxin treatment when its availability is limited especially in outbreaks where the number of patients is large and unpredicted. This was contradictory to O’Horo et al. (2017), in their systematic review, as they could not identify patients likeliest to benefit from the antitoxin treatment. But this was in agreement with Anderson et al. (2019) and Barker et al. (2019) who started the BAT after the appearance of the confirmed signs of intoxication.

In addition, after receiving the first dose of HBAT, 17.7% of the cases showed no improvement and 26.4% showed temporary improvement and relapsed later which necessitated the administration of further HBAT doses. These results may be explained by the mechanism of HBAT; it interacts only with an unbound toxin, and patients who admitted early were improved on one vial, while those who arrived late needed second and third vials and 2 of them died in the hospital (O’Horo et al. 2017; Anderson et al. 2019; Barker et al. 2019). Those who suffered rebound after initial improvement were mentioned in a study of Fagan et al. (2011).

The only drawback of the current protocol is the prolongation of hospitalization due to monitoring of the patients which reaches up to 12 days in some cases to avoid missing the unpredicted side effects of the antitoxin.

In the current study, following the theory of starting the BAT after specific confirmed signs, complete recovery occurred in 87.2%. Complications were present in 10.6% of patients while death occurred only in two cases (2.2%). All those 10.6% of patients were discharged with complications received the HBAT. They complained of persistent dry mouth with a very mild dysphagia not interfering with fluid, solid, or semisolid food ingestion. Some complained of constipation which improved also with the usage of laxatives. This is similar to the study of Gottlieb et al. (2007) who concluded that previous symptoms of a cholinergic autonomic blockade that are prominent during botulism as dry mouth would persist for a long term later.

Regarding the two cases who died, both were in group C1 with evident neurological paralysis, and according to their history, the muscle weakness started before arrival to hospital by more than 4 h as they came from remote govern mates. They received a single dose of the antitoxin, and both were in need for mechanical ventilation in ICU. They arrested in the ICU; the one after 2 days and the other after 4 days without receiving any further doses of HBAT as these two patients were at the start of the outbreak and we were following the instructions in the pamphlet of the antitoxin that recommended only single dose of the antitoxin, and it states that the second dose may not show any further improvement, so we saved further doses for other patients. It is important to clarify that it was the first time to use HBAT. In the past, trivalent botulinum antitoxin was available instead. At the beginning, we were committed to Cangene pamphlet instructions, then we tried to give further doses up to three vials based on the clinical examination which showed improvement in patients who received them.

However, according to the critical care physicians, the cause of death in these two patients was a superadded chest infection. This point is very important as the appropriate supportive care is still the cornerstone in recovery and survival after botulism. As those cases suffered respiratory compromise, so high-quality intensive care is needed. This is in accordance with Sheth et al. (2008).

Conclusions

Based on the previous results, cases with suspected botulism often have a stationary course. A total of 63.8% of our cases were managed by supportive treatment with no need for HBAT. So it is advised to keep such patients under close observation instead of hastily giving the antitoxin. Patients with one or two symptoms of autonomic dysfunction should only remain under observation and if they develop a third symptom, the antitoxins should be administered as was done in 77.8% of our cases. Administer the antitoxin at first intension for patients with four autonomic symptoms or evident neurological manifestations.

Availability of data and materials The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Author contribution Sara A. Ghitani participated in the design of the study, drafted the manuscript, and participated in reviewing its final version; Maha A. Ghanem participated in data collection and in drafting the manuscript and reviewing the final version; Eman A. Sultan participated in the design of the study and performed the statistical analysis; Maii F. Henaidy participated in writing the results section.

Declarations

Ethics approval and consent to participate Approval was obtained from the Research Ethics Committee of Faculty of Medicine, Alexandria University (IRB NO:00012098, FWA NO: 00018699, serial protocol NO:0304565).

Adherence to national and international regulations The Ethics Committee is constituted and operates according to ICH GCP Guidelines and applicable local and institutional regulations and guidelines that govern ethics committees’ operation.

Consent for publication Not applicable as the research didn’t include any individual person’s data in any form.

Competing interests The authors declare no competing interests.
References

Anderson DM, Kumar VR, Arper DL, Kruger E, Bilir SP, Richardson JS (2019) Cost savings associated with timely treatment of botulism with botulism antitoxin heptavalent product. PLoS One 14(11): e0224700.

Barker D, Gillum KT, Niemuth NA, Kodihalli S (2019) Therapeutic efficacy of equine botulism heptavalent antitoxin against seven botulinum neurotoxins in symptomatic guinea pigs. PLoS One 14(9): e022670.

Chaudhry R. (2011) Botulism: A Diagnostic Challenge. Indian J Med Res 134(1):10-2.

Fagan RP, Neil KP, Sasich S, Laquez C, Asaad H, Misakian A et al. (2011) Initial recovery and rebound of type E intestinal colonization botulism after administration of investigational heptavalent botulinum antitoxin. Clin Infect Dis 53(9): e125-e128.

Fleck-Derderian S, Shankar M, Aoak AK, Chatham-Stephens K, Adjei S, Sobel J et al. (2017) The epidemiology of foodborne botulism outbreaks: a systematic review. Clin Infect Dis 66(suppl_1): S73-S81. DOI: https://doi.org/10.1093/cid/ciz846.

Gaware VM, Kotade KB, Dolas RT, Dhamak KB, Somawanshi SB, Fleck-Derderian S, Sobel J (2008) International outbreak of severe botulism with prolonged toxemia caused by commercial carrot juice. Clin Infect Dis 47:1245–51.

Sobel J. (2009) Diagnosis and treatment of botulism: a century later, clinical suspicion remains the cornerstone. Clin Infect Dis 48: 1674–75.

Sheth AN, Wiersma P, Atrubin D, Dubey V, Zink D, Skinner G, Staubesand G (2015) Intussusception in infant with diagnostic botulism: a case report. Arch Argent Pediatr 113(5): e286-9. https://doi.org/10.1016/j.arcped.2015.02.003.

Veterinarians warn of the mass death of fish in Lake Rashid (2019) Veterinarians warn of the mass death of fish in Lake Rashid. (2019) https://www.cnn.com/2019/09/27/middleeast/fish-slaughter-lake-lake-rashid-morten-yn-stueste-intl-spt/index.html.

Wheeler C, Inami G, Mohle-Boetani J, Vugia D (2009) Sensitivity of mouse bioassay in clinical wound botulism. Clin Infect Dis 49:1669-73. https://doi.org/10.1086/599029.

Yu P. (2015) Heptavalent botulinum antitoxin (BAT) use in patients treated under CDC’s expanded access IND, 2010–2013. Atlanta: CDC.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.