CLINICAL PRACTICE ARTICLE

Botulism outbreak after the consumption of vegetarian pâté in the south of Viet Nam [version 1; peer review: 1 approved with reservations]

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Abstract

Botulism is a potentially life-threatening disease caused by toxins produced by *Clostridium botulinum*. Here we reported a case series of six patients who presented with botulism following ingestion of commercially made pâté. The key features of presentation were acute onset of bilateral cranial nerve palsies and symmetrical descending weakness in the absence of fever resulting in the need for mechanical ventilation in all six patients. The clinical diagnosis of botulism was confirmed through the identification of *C. botulinum* from the suspected food source. Given that botulinum antitoxin was not available in Vietnam at the time, and their severe status, all patients received a trial of plasma exchange therapy, but no clear benefit was seen.

Due to its rarity, diagnosing botulism is a challenge, demanding high clinical suspicion. Successful outcomes depend upon early recognition and rapid initiation of specific treatment with botulinum antitoxin. There is a need to improve global access to antitoxin. These cases, the first in Viet Nam, serve as a reminder of the need to maintain the highest possible food hygiene and preservation practices.

Keywords

Botulism, botulinum toxin, *Clostridium botulinum*, pâté

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Introduction

Botulism is a neurotoxin-mediated illness caused by the gram positive, anaerobic, spore-forming bacillus *Clostridium botulinum* (*C. botulinum*), which occurs naturally in soil and sediments. Foodborne botulism follows the ingestion of food contaminated with one of a number of the described toxin subtypes, and is the commonest form of human botulism^{1,2}. Typically, foodborne botulism occurs following the consumption of domestically canned, low acid-containing foods³. Examples of such home-canned foods include vegetables, seafood (fermented fish and smoked fish), and dairy products⁴. However, botulism outbreaks have also been described where the source has been commercial food products⁵. Less frequently, botulism can arise following injuries which result in wound inoculation or contamination with *C. botulinum*. Here, unlike in food-borne botulism, toxin production occurs within the human host. Rarely, infant botulism occurs due to colonization of the gut by *C. botulinum*, again resulting in endogenous toxin production.

The botulinum toxin exerts its effects within neurons by inhibiting the fusion of acetyl choline containing pre-synaptic vesicles with the cell membrane, thus preventing the release of the neurotransmitter⁶. This presents clinically as a flaccid paralysis, and the classical manifestation of botulism is described as an acute onset of bilateral cranial neuropathies with a symmetrical descending paralysis. Fever is not a feature. Definitive diagnosis depends upon the detection of botulinum toxin, or isolation of *C. botulinum*, from both clinical and source (food) samples. The diagnosis of possible botulism can be made based upon a typical presentation and a contact history. Foodborne botulism has been documented in Europe since the eighteenth century⁷. However, in Viet Nam, botulism has not previously been described. This may be genuine, perhaps due to food practices, or represent under-reporting – the diagnosis may be missed due to low index of suspicion or overlap of symptoms with other neurological syndromes. Importantly, the specific treatment for botulism – antitoxin – is not always available in Viet Nam. Delay in diagnosis and lack of specific treatment are likely to result in worse clinical outcomes. Here, we report six patients who presented to our hospital with symptoms suggestive of botulism following consumption of a commercially produced vegetarian pâté. To our knowledge, these are the first cases of botulism reported from Viet Nam, and also the first outbreak associated with vegetarian pâté.

Case presentation

On July 24, 2020, case 1, a Taiwanese 36-year-old male, working as a hotel staff presented to our Department of Tropical Diseases, Cho Ray hospital, Ho Chi Minh City. He had been referred from his local hospital in Khanh Hoa province, south central coast of Viet Nam where he had been admitted 4 days previously with a one-day history of nausea and vomiting. There was no history of fever. Over the ensuing four days at Khanh Hoa he developed progressive dizziness, blurred vision, dysphagia and bilateral ptosis. On arrival at Cho Ray hospital, he was found to have dysarthria and complained of mild breathlessness. There was no recent travel. He reported

consumption of seafood one day prior to the onset of the original symptoms (mussels, clams and obtuse horn shells). On physical examination, he was alert, breathing spontaneously, and had bilateral ptosis, worse on the right side. His pupils appeared normal. Limb power was normal. Due to his history of seafood ingestion, the initial differential diagnosis was saxitoxin, brevetoxin or tetrodotoxin poisoning, with consideration also given to Guillain-Barré syndrome.

The second case was the wife of case 1. She was a Vietnamese 36-year-old female factory worker in the second trimester of pregnancy and had accompanied her husband to our hospital. She had consumed the same seafoods at the same time as her husband, and had had similar gastrointestinal symptoms one day later. She had not previously received a hospital assessment. However, as her husband was being assessed she mentioned she now had blurred vision and dysphagia. On examination she was found to have bilateral ptosis and was admitted with her husband.

Laboratory evaluations for both patients, including complete blood cell counts, and serum level of sodium, potassium, blood glucose, blood urea nitrogen and creatinine were normal. Cranial computed tomography and magnetic resonance imaging were normal. Both patients underwent lumbar punctures; cerebrospinal fluid analyses were unremarkable. Both patients underwent electromyography which showed low-voltage compound motor-units, consistent with axonal neuropathy. The possibility of Guillain-Barré syndrome was suggested in the differential diagnosis. Three days following hospital admission the condition of both cases had deteriorated, with descending quadriparesis, and worsening respiratory function. Foodborne botulism was suspected and the dietary history re-explored from their relatives. This revealed that the couple had eaten the same brand of jarred vegetarian mushroom pâté produced in Viet Nam approximately 20 to 36 hours before the first symptoms occurred.

Cases 3, 4 and 5 were three Vietnamese women aged 20, 24 and 26, respectively, again referred to our department from their local hospitals at the end of July 2020. The three were friends and worked as office staff for a company in Dong Nai province. The cases had no social link to cases 1 and 2 and lived approximately 400 kilometers from them. They gave a history of gastrointestinal symptoms (nausea, vomiting and abdominal pain) followed by the development over the next 2 days of neurological deficits including dysarthria, bilateral ptosis, difficulty in breathing and limb weakness (strength 2-3/5 Medical Research Council grade). One patient had reported a mild fever on the first day of illness. All 3 patients underwent lumbar puncture, routine hematological and biochemical investigations, and brain computed tomography scan in our hospital, and all these were unremarkable. Because of the similarity of their presentations with cases 1 and 2, a detailed history of food consumption was taken. They had eaten the same brand of vegetarian pâté as the previous couple between 24 and 48 hours before the appearance of their symptoms. Clinical specimens obtained from all 5 patients (serum and stool), and samples

of suspected food (the remainder of the canned pâté at their house), were sent to the Institute of Hygiene and Public Health, Ho Chi Minh city. The presence of *Clostridium botulinum* in the food samples of all cases was confirmed by bacterial culture method and the diagnosis of botulism was established. *C. botulinum* was not isolated from patient specimens.

The last case was a 54-year-old Vietnamese salesman who presented to our department in August approximately 3 weeks after the first 5 cases. He gave a history of dizziness, nausea, vomiting and abdominal pain which occurred 24 hours after eating the same brand of vegetarian pâté. Over the next 24 hours, he developed double and blurred vision, bilateral ptosis, dysarthria, dysphagia and a descending paralysis. Laboratory investigations including complete blood count, urea and electrolytes were normal. Cerebrospinal fluid examination was normal. Now with a high index of suspicion, the diagnosis of botulism was made promptly. The clinical and laboratory findings of all cases are summarized in [Table 1](#) and [Table 2](#).

Treatment and progress

All six cases required intubation and mechanical ventilation due to weakness of respiratory musculature. The median time to intubation and mechanical ventilation following consumption of the pâté was 6.5 days (range 4 to 9 days). Botulinum antitoxin was not available in Vietnam at the time. Because of the severe deteriorating status of the patients, and the lack of antitoxin, we administered therapeutic plasma exchange (TPE) in addition to standard supportive therapy. TPE was administered on alternate days on 3 occasions during the third week of hospitalization for each of the first 5 cases, and during the first week of hospitalization for the sixth case. Amongst the first 5 patients, immediately following TPE four showed recovery of ptosis and

some improved limb strength sufficient to warrant attempts at weaning from ventilation. However, there did not appear to be any long-lasting/permanent benefit of TPE in any patient. We could not detect any benefit of TPE in the 6th patient.

All patients underwent tracheotomies after 14 days of intubation. The first five cases remained in our hospital for 4 to 5 weeks to referral back to their local hospitals for on-going intensive care unit care. All patients required on-going invasive mechanical ventilation when discharged. The sixth patient remains in intensive care in our department. [Table 3](#) details the conditions of all the cases at the time of this report.

In addition to these six cases, seven further cases of botulism were identified during this time. These patients had similar clinical manifestations to the six reported here, and also had eaten the same brand of vegetarian pâté as our patients. In two of these seven cases, *Clostridium botulinum* was detected in both clinical samples (stool) and pâté. None of these additional cases received botulinum antitoxin until the beginning of September when this was kindly provided by the World Health Organization. The antitoxin was administered after at least 4 weeks of illness for 10 of 13 patients (by this time, cases 2, 4 and 5 described above had been successfully weaned from mechanical ventilation; hence, they did not receive antitoxin). The recovery of the remaining 13 patients is ongoing.

Discussion

This is the first case report of an outbreak of botulism in Viet Nam. It demonstrates the need for a high index of suspicion in order to make the diagnosis in a timely manner, the severe associated morbidity, and the need to have rapid access to antitoxin.

Table 1. The summary of clinical findings of six cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, gender	36, male	36, female	20, female	24, female	26, female	54, male
Time interval from ingestion to the symptom onset	21 hours	36 hours	24 hours	48 hours	48 hours	24 hours
Nausea, vomiting	yes	yes	yes	yes	yes	yes
Abdominal pain	no	no	yes	yes	yes	yes
Blurred, double vision	yes	yes	no	no	no	yes
Dysarthria	yes	yes	yes	yes	yes	yes
Dysphagia	yes	yes	yes	yes	yes	yes
Ptosis	yes	yes	yes	yes	yes	yes
Dyspnea	yes	yes	yes	yes	yes	yes
Limb weakness	yes	yes	yes	yes	yes	yes
Fever	no	no	no	no	no	no
Impaired consciousness	no	no	no	no	no	no

Table 2. The summary of laboratory investigations.

Lab tests (unit, normal range)	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Hemoglobin (g/dL, 12–17)	14.8	11.4	13.0	12.8	13.6	15.5
White blood cell (/mm ³ , 4000–11000)	8060	9880	2920	14000	6250	11500
Neutrophil (%)	64	83	73	86	75	82
Platelet (/mm ³ , 200000–400000)	239000	268000	167000	230000	227000	249000
Aspartate transaminase (U/L, 5–49)	22	23	19	19	47	22
Alanine transaminase (U/L, 9–48)	14	27	14	29	38	21
Blood urea nitrogen (mg/dl, 7–20)	23	7	8	13	12	28
Creatinine (mg/dl, 0.7–1.5)	2	0.37	0.58	0.6	0.68	0.82
Lactate dehydrogenase (U/L, 200–400)	168	143	235	197	161	432
Creatin phosphokinase (U/L, 34–171)	205	Not done	37	Not done	Not done	81
Urine myoglobin (ng/ml, <5)	>1000	8.37	8.87	8.9	19.8	7.7
CSF ¹ Cell count (/mm ³ , <5)	0	1	1	1	1	1
CSF ¹ Protein (mg/dl, 15–45)	38	6.5	15	21	37.5	29.5
CSF ¹ /blood glucose (mg/dl, >0.5)	57 / 116	58 / 98	89 / 130	90 / 152	67 / 112	74/117
PCR CMV and EBV ²	Negative	Negative	Negative	Negative	Negative	Not done
Electromyography	The motor axonal neuropathy;	The motor axonal neuropathy; and test for myasthenia gravis negative	The motor axonal neuropathy	The motor axonal neuropathy; and test for myasthenia gravis negative	The motor axonal neuropathy	The motor axonal neuropathy; and test for myasthenia gravis negative
Electroencephalography	Normal	Normal	Normal	Not done	Not done	Not done
Cranial MRI ³ and CT ⁴ scan	Normal	Normal	Normal	Normal	Not done	Normal
Food samplings	Isolation of <i>Clostridium botulinum</i>					

Note: ¹: Cerebrospinal fluid, ²: Polymerase chain reaction of Cytomegalovirus and Epstein-Barr virus, ³: Magnetic resonance imaging, ⁴: Computed tomography.

Botulism is caused by *C. botulinum* through the action of botulinum neurotoxins (BoNTs). BoNTs are divided into several toxinotypes (A, B, C, D, E, F, G, H, and F/A) and each toxinotype is further divided into subtypes. Until now, 41 such subtypes have been described⁸. The sophisticated understanding of the complexity of the toxin subtypes is at odds with our ability to diagnose foodborne botulism, which depends in the first instance upon clinical suspicion based upon the history and clinical signs. There are no rapid tests available to aid diagnosis at the time of presentation. Confirmation of diagnosis comes through epidemiological investigation to identify potential exposure, with microbiological confirmation of the presence of the organism or toxins in the source +/- patient samples. As seen in our cases, identifying the organism in human clinical samples has low sensitivity. Epidemiological confirmation of the diagnosis takes considerable time; given that a potentially effective antitoxin is available, the development of more sensitive and more rapid diagnostics would be welcomed, particularly in settings such as the tropics where other foodborne neurotoxins are prevalent.

The incubation period of botulism can range from several hours to a week⁹. The presentation of our cases was typical and consistent with previous studies, but we saw some variability in the time to development of life-threatening neurological compromise. The first symptoms involved the digestive system and included nausea, vomiting and abdominal pain. These usually appear within 12 to 36 hours of ingestion of the food source⁹. However, both the gastrointestinal and neurological symptoms may be delayed by as much as eight days after exposure¹⁰. The variability in presentation may represent a dose effect of the botulinum toxin. Our experience offers circumstantial evidence supporting this. In our series, case 2, who had eaten smaller amounts of pate compared with her husband, had a relatively delayed presentation, with neurological signs occurring on day 5, in contrast to after 24 hours as seen in her husband. A recent report of two cases from Germany, describes a similar finding. Here, the patient who had ingested a smaller amount of contaminated food developed descending paralysis later than the other¹¹. However, while variability in the time to onset of symptoms appears to depend on how much contami-

Table 3. Assessment of the recovery of six cases at discharged.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Time interval from onset to assessment (days)	33	33	30	28	27	14
Blurred vision	no	no	no	no	no	yes
Dysarthria, dysphagia	Assessment was not obtained					
Ptosis	no	yes	yes	mild	mild	yes
Spontaneously breathing	yes	yes	no	yes	yes	no
Weaning from mechanical ventilation	Periodically	Periodically	Totally depending on mechanical ventilation	Periodically	Periodically	Totally depending on mechanical ventilation
Limb weakness	5/5	5/5	2/5	3-4/5	4-5/5	2-3/5
Days of hospitalization	34	34	31	29	27	Has not been discharged yet
Days of ventilation	31	31	31	31	26	Has not been discharged yet
Ventilation at discharged	yes	yes	yes	yes	yes	Has not been discharged yet
General assessment by attending doctors	Moderate recovery	Moderate recovery	Re-paralysis after 2 days of improvement	Mild recovery	Mild recovery	Not changed

nated food has been eaten, the huge potency of the toxin resulted in all patients in our series ultimately requiring intubation and mechanical ventilation¹².

The presentation of botulism can be subtle. The earliest neurological symptoms tend to involve the eyes, with blurred and double vision, and ptosis¹³. These maybe followed by dysarthria, in turn, followed by progressive weakness of limb muscles and respiratory insufficiency. Around 68% of cases of foodborne botulism present with simultaneous neurological and gastrointestinal symptoms¹³. Autonomic dysfunction can also be an important clue to botulism. Symptoms and signs may include resting tachycardia, supine hypertension, and orthostatic hypotension, explained by inhibition of the parasympathetic nervous system. Such autonomic dysfunction is thought to be particularly associated with botulism type B, the absence of such symptoms/signs in our patients suggest an alternative toxin subtype was responsible¹⁴.

Botulism should be considered within a broad differential diagnosis, including seafood poisoning (brevetoxin, saxitoxin, ciguateratoxin), heavy metal intoxication, myasthenia gravis, tick paralysis, Guillain barre, Lambert–Eaton syndrome, poliomyelitis/Japanese encephalitis, and stroke¹⁵. A detailed history investigating potential exposures, the health of contacts, and the disease progress, are crucial in obtaining the correct diagnosis.

Lambert–Eaton and myasthenic syndrome can be excluded by electromyography and antibody studies. Guillain–Barre syndrome usually involves an ascending rather than descending paralysis, associated sensory findings, and an elevated cerebrospinal fluid protein.

Identifying the food source of botulism is crucial in confirming the diagnosis and managing the risk to public health. Improper food storage and preservation can provide specific conditions such as the anaerobic, low salt, low acid environments which facilitate the growth and development of the toxin producing *C. botulinum*. Identification of the food source should lead to an examination of food handling practices with education and remediation as needed. The vegetarian pâté consumed by our patients contained nuts (almond, walnuts, cashew), and mushroom, was produced in metal containers which were able to provide the anaerobic conditions needed for bacterium growth and toxin production.

Key to the diagnosis of botulism in our case series was the presentation of multiple patients with consistent syndromes. However, we were unable to isolate *C. botulinum* from any clinical specimen. Identifying sporadic cases affecting only single individuals remains extremely challenging, requiring a high index of suspicion; developing more rapid, sensitive, and affordable tests would enable a better understanding of the

epidemiology of this disease and the more timely intervention of treatment.

While the rarity of disease means no randomized controlled trials have been performed, it is believed that administration of antitoxin can shorten hospital stay and decrease the duration of mechanical ventilation¹⁶. The benefit of antitoxin depends on neutralization of that toxin which is unbound to neuromuscular junctions, and this requires administration within the first 24 hours of presentation^{17,18}. However, it must be noted that there is no constraint for the latest time of effective antitoxin administration (see WHO botulism factsheet), with benefit having been reported in patients treated with antitoxin up to 8 days after the onset of symptoms¹⁹.

Unfortunately antitoxin was not available in Vietnam when we received the cases reported here, and given their severe condition this led us to try TPE, which has been used to treat myasthenic-type crises following therapeutic Botox injections²⁰. The first five of our cases underwent TPE in the third week of illness and we observed clinical improvement in 4 of 5 cases. However, it is impossible to tell whether this was the normal disease course or due to the intervention, and contrasts with the sixth case who received TPE on three occasions in the first week of disease. Early intervention might be expected to be more effective but we could discern no clinical improvement in muscle strength following the treatment. Other treatments suggested for botulism have included dalfampridine or 4-aminopyridine,

prescribed to control symptoms in multiple sclerosis. This drug has been used in some cases of severe botulism, and offered some signs of enhancement in peripheral muscle strength, but it needs further study²¹.

Conclusion

We report the first recognized outbreak of botulism in Vietnam. All patients were severely unwell and ultimately required mechanical ventilation. Diagnosis requires a high index of suspicion, and has to be distinguished from other intoxications that are more common in tropical climates, such as those associated with seafood. The syndrome should be considered in patients presenting with absence of fever, a normal conscious level, and an acute descending paralysis. Detailed exposure history is essential to identify sources that may be continuing to put the wider community at risk. The logistics of maintaining stocks of costly antitoxin for what are rare diseases is a challenge; cross-border cooperatives with rapid dissemination of stocks as needed may be one solution.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details was obtained from the patients.

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The manuscript of Thi Tuy Ngan *et al.* reports the first outbreak of food borne botulism which has been confirmed in Vietnam. Food-borne botulism is rare but it is the most severe food intoxication which is often lethal without treatment. Here, the authors describe a botulism outbreak including six patients. The clinical symptoms, treatment, and outcomes are reported for each patient. All the patients were hospitalized in an intensive care unit with mechanical ventilation. Laboratory investigations include regular hematology analysis, cerebrospinal fluid analysis, electromyography, cranial computed tomography, magnetic resonance imaging, as well as food analysis. The diagnosis of botulism was suspected based on the epidemiological investigations showing that the six patients and seven additional patients ate the same food. It was pointed out that anti-botulinum serum, which is the only specific treatment of botulism, was not available in Vietnam and that global access to antiserum is required.

It is indicated that the incriminated food is a vegetarian mushroom paté. More details are required about the preparation of this food: industrial, small scale, or home-made product? Date of preparation of the food and dates of consumption of the food by the patients? Recommended conditions of storage of this food? How this food was preserved, room temperature, low temperature? Which is the possible origin of food contamination?

Laboratory investigations. It is indicated that *Clostridium botulinum* was confirmed in food but not in patient's specimens. More details about the identification of *C. botulinum* are required: by which method *C. botulinum* has been identified in food? Which is the *C. botulinum* typing? Botulinum typing is important to adapt specific antiserum for eventual treatment by serotherapy. Has botulinum toxin been investigated in food? Which patient's specimens have been investigated for botulism? Usually, *C. botulinum* and botulinum toxin are investigated in stool samples and botulinum toxin in serum sample.

Is the background of the cases' history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the conclusion balanced and justified on the basis of the findings?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clostridial toxins including botulinum toxins

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Dec 2020

Ngan Thi Thuy Nguyen, Oxford University Clinical Research Unit, Ho Chi Minh city, Vietnam

Questions: It is indicated that the incriminated food is a vegetarian mushroom pâté. More details are required about the preparation of this food: industrial, small scale, or home-made product? Date of preparation of the food and dates of consumption of the food by the patients? Recommended conditions of storage of this food? How this food was preserved, room temperature, low temperature? Which is the possible origin of food contamination?

Answer: The vegetarian pâté consumed by all cases was made by a small-scale family-run business using locally-sourced ingredients and handmade methods. Pâté bought by the first 5 cases and the sixth case were prepared separately in July 2020 and August 2020 respectively. All consumption of pate occurred within the use-by dates (December 2020 and January 2021 respectively). The manufacturer recommended the product be stored frozen and the expiration date was 6 months following production. All cases told us they kept once-opened pâté at room or fridge temperature (5-10 °C). The exact source of contamination during the production process is not clear.

We also added this information into the new version of manuscript.

Question: Laboratory investigations. It is indicated that *Clostridium botulinum* was confirmed in food but not in patient's specimens. More details about the identification of *C. botulinum* are required: by which method *C. botulinum* has been identified in food? Which is the *C. botulinum* typing? Botulinum typing is important to adapt specific antiserum for eventual treatment by serotherapy. Has botulinum toxin been investigated in food? Which patient's specimens have been investigated for botulism? Usually, *C. botulinum* and botulinum toxin are investigated in stool samples and

botulinum toxin in serum sample.

Answer: C. botulinum was identified in the food product according to the mouse bioassay method of Association of Official Analytical Chemists (AOAC) 977.26. Unfortunately, we do not currently have the facility to detect and type C. botulinum toxin.

The diagnosis of botulism was made in our patient clusters because of the consistent clinical syndrome and the isolation of C. botulinum from pâté, consumed by all patients. We were unable to isolate C. botulinum from any patient specimen and lacked the resources to isolate the toxin. However, we think the clinical, epidemiological and microbiological evidence associated with our patients is sufficient to allow us to be confident in our diagnosis. We addressed the limitations of our diagnostic methods in the discussion. We agree there is a need for improved, sensitive and specific point of care and laboratory tests which would enable rapid diagnosis and treatment, also addressed in our discussion.

Competing Interests: No competing interests were disclosed.