Case Series

Foodborne botulism outbreak with potential new management options

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ABSTRACT

الأهداف: إلقاء بعض الضوء على طريقة علاجية محتملة تساعد في حل أعراض التسمم الغذائي، وهي 3,4- ديامينوبيريدين (3,4-DAP).

المنهجية: في الرياض، المملكة العربية السعودية، واجهنا مؤخرًا تفشي التسمم الغذائي الذي ينتقل عن طريق الغذاء، والذي تم اكتشافه مبكرًا، لحسن الحظ. وفي مدينة الأمير سلطان الطبية العسكرية، استقبلنا، خلال فترة 3 أسابيع تقريبًا، 15 حالة محتملة، تم استبعاد حالتين منها بسبب تشخيصات بديلة أكثر احتمالية. نستعرض في هذه التقرير 13 حالة مشتبه بها للغاية من حالات التسمم الغذائي التي واجهناها أثناء تفشي المرض.

النتائج: احتاج 12 من أصل 13 مريضا يحتاجون إلى دخول وحدة العناية المركزة (ICU)، أحدهم احتاج إلى التنبيب. وشملت الأعراض شلل العصب القحفي، وأعراض الجهاز الهضمي، وضعف الأطراف وعضلات الجهاز التنفسي. أظهر المرضى تحسنًا سريريًا عند تلقيهم مضاد سموم البوتولينوم و3,4-DAP إذا تم إعطاؤهم في وقت مبكر من مسار المرض.

الخلاصة: اظهرت الدراسة أن العلاج المبكر لـ 3,4-DAP يساعد على الشفاء ومنع تطور المرض. وينبغي إجراء تجارب مستقبلية أكبر تؤكد ذلك.

Objectives: To shed some light on a potential therapeutic modality that may facilitate resolution of botulism symptoms, namely 3,4-diaminopyridine (3,4-DAP).

Methods: In Riyadh, Saudi Arabia, we recently encountered a foodborne botulism outbreak that, luckily, was discovered early. In Prince Sultan Military Medical city, we admitted, during a period of approximately 3 weeks, 15 probable cases, 2 of which were excluded due to more likely alternative diagnoses. We report in this case series 13 highly suspected cases of botulism that we encountered during the outbreak.

Results: A total of 12 out of 13 patients required intensive care unit (ICU) admission, one of which required intubation. Symptoms included cranial nerve palsies, gastrointestinal symptoms, limb and respiratory muscle weakness. Patients showed clinical improvement when received botulinum antitoxin and 3,4-DAP if given early in the course of the disease.

Conclusion: Early admisntration of 3,4-DAP may facilitate recovery and prevent disease progression. Larger prospective trials should be carried out to confirm that.

Keywords: outbreak, botulism, paralysis, antitoxin, 3,4-diaminopyridine

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Botulism is an uncommon, potentially life-threatening, flaccid descending paralysis.[1] It usually starts with paralysis of several cranial nerves, then descends to the limb muscles and usually ends with respiratory muscle weakness that, if untreated, may result in apnea and death. It is usually caused by contamination of food by botulinum toxin (foodborne botulism) which, if ingested, irreversibly binds to the presynaptic portion of the junctions of peripheral and autonomic nerves.[2] This will block the release of acetylcholine at these junctions resulting in flaccid paralysis of supplied muscles. Because of its large size, the toxin does not cross the blood brain barrier and therefore, there is no central nervous system involvement.[1] This neurotoxin is produced mainly by *Clostridium botulinum*, an anaerobic, gram positive, spore-forming bacteria that multiply under certain

circumstances in contaminated stored food, particularly canned and home-processed food (Figure 1).[3]

Epidemics rarely happen and are usually related to foodborne botulism that can be traced to a particular source (namely, a restaurant or a food product). Small outbreaks are more likely and are usually related to home-processed food. Furthermore, and due to the life-threatening nature of the disease, such epidemics and outbreaks are considered as public health emergencies. Therefore, there should be established national disaster response plans to deal with such outbreaks as cases may overwhelm the critical care areas of specific health care institutes.[1]

We report in this case series 13 highly suspected cases of botulism that we encountered during the outbreak. We will try to shed some light on a potential therapeutic modality that may facilitate resolution of botulism symptoms, namely 3,4-diaminopyridine (3,4-DAP).

Methods. We recently encountered the outbreak of foodborne botulism in Riyadh, Saudi Arabia. A total of 75 suspected cases of botulism were managed in several health care institutes in Riyadh in April and May 2024, most of which required intensive care unit (ICU) admission at the course of the illness (Figure 2). In this case series, we are publishing 13 highly suspected cases of botulism that got admitted to Prince Sultan Military Medical city in Riyadh, Saudi Arabia, the majority of which are linked to the same food source. This case series is retrospective and complies with the Declaration of Helsinki. The cases were diagnosed based on epidemiologic data, clinical features suggestive of botulism, and response to specific therapy. Although confirmatory laboratory samples were carried out, we did not receive the results until the date of submission of this paper.

These cases were mainly linked to a particular food source (a restaurant). Health care authorities in Riyadh, Suadi Arabia, did all necessary measures to identify the source of contamination and limit the spread of the disease. Out of the 75 cases encountered in Riyadh, 50 cases were actually confirmed using specific laboratory tests. As of May 3, 2024, 20 patients out of 75 remained in ICU and 43 were discharged home in good conditions (Figure 2).

Considering the nature of the study, only descriptive analysis is used displayed as numbers and percentage.

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Figure 1 - Home-made and home-stored canned food (pickles).

Results. A total of 15 suspected cases of botulism were admitted to Prince Sultan Military Medical city in Riyadh, Saudi Arabia, between April 18th and May 5th, 2024 (Table 1). Two of these cases were eventually excluded based on clinical grounds as other more likely diagnoses were considered (Figure 3). The remaining 13 cases were included in this case series analysis as they remain highly suspected from the clinical stand point. Laboratory specimens were carried out for all 15 cases but we do not have the final results until the submission of this paper.

All 13 cases included in the study were relatively young and the majority were below the age of 30, (Table 2). Two thirds were males and none of them had significant co-morbidities. Around half of the patients ate from food source-1 and a quarter ate from food source-2. The remaining ate from random food sources. All food sources involved are, in fact, fast-food restaurants.

The period from exposure to the development of symptoms varied among patients, but mostly was within several hours, not exceeding 48 hours (Table 2). The most commonly encountered symptoms in our cases were cranial nerve palsies and gastrointestinal symptoms followed by respiratory and limb muscle weakness (Table 2). First few patients were initially suspected to have myasthenia gravis (MG) or Guillain-Barré syndrome (GBS) and were investigated and managed as such until botulism was considered and management plan changed. As an example, patient-1 is considered as a potential botulism case 7 days following admission. This is expected as the outbreak was not yet announced then. Similarly, several patients at the beginning of the

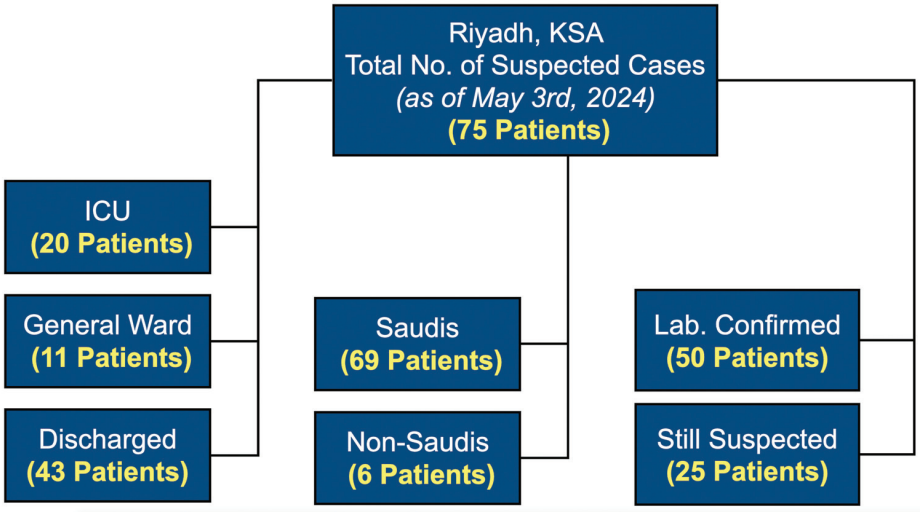

Figure 2 - Statistics of cases in Riyadh as of May 3, 2024 as per announcement carried out by Ministry of Health on that date. KSA: Kingdom of Saudi Arabia, ICU: intensive care unit, Lab.: Laboratory

outbreak were managed as GBS or MG and were given intravenous immunoglobulin (IVIG) and the majority did not show subjective or objective improvement to that (Tables 1 & 2). The botulinum antitoxin was given late to the first 3 patients (patients 1-3), as the diagnosis was not clear then. The remaining patients received the antitoxin at day 0 (Table 1). There is subjective improvement following administration of the antitoxin in most patients. No adverse reactions reported (Table 2).

A total of 12 patients received oral 3,4-DAP which was traditionally used in the management of Lambert-Eaton myasthenic syndrome (LEMS). 3,4-Diaminopyridine enhances the release of acetylcholine at the neuromuscular junctions and, hence, improves muscle power. We found that 10 out of the 12 patients who received 3,4-DAP reported subjective improvement (Table 2). Although, no one can tell if the improvement is related to 3,4-DAP, the antitoxin or other factors, it is of note that several patients volunteered that they noticed improvement few hours after taking 3,4-DAP. Two patients developed mild cardiovascular symptoms after 3,4-DAP administration (Tables 1 & 2).

A total of 12 patients required ICU care, one required intubation and mechanical ventilation (MV; patient 2). Two patients required high flow nasal cannula or non-invasive ventilation. A total of 11 patients were discharged home in good conditions and one patient is still in ICU, on MV (patient 2) and another is in rehabilitation ward (patient 10). If we exclude patient 2, the ICU-length of stay (LOS) ranges from 2-9 days, average of 4 days, and if we exclude patients 2 and 10, the hospital LOS is 2-19 days, average of 7 days, (Tables 1 & 2). No mortalities until the submission of this paper.

Discussion. Botulism is a rare neurotoxin-induced muscle paralysis disorder that, if untreated, may result in respiratory failure and death.[1] Outbreaks and epidemics are extremely uncommon but if took place, they are considered health care national emergencies as the disease is potentially lethal. The food source may take some time to be identified and controlled.[1] In Saudi Arabia and based on published data, including CDC data, this outbreak could be the first of its kind. Therefore, days were required to entertain more common similar conditions (namely, MG and GBS), until botulism was actually considered and investigated for. In fact, few patients underwent various neuro-imaging studies, nerve conduction studies, electromyography, and even lumbar punctures at the start of the outbreak. Some also received treatment for such conditions, like IVIG.

When botulism came into the differential diagnosis, the Ministry of Health (MOH) traced the cases and most were linked to a certain fast-food restaurant (source-1). Some of the cases that presented afterward had no history of consuming food from that particular restaurant. This suggests that other restaurants may be involved or that the distributor of a certain food material is possibly responsible. Consequently, less and less cases were being reported as days passed but the health care system in Riyadh, Saudi Arabia, was at its peak alert for any new wave of botulism during this outbreak.

In this case series, all patients were considered to be cases of confirmed or, at least, highly suspected

Table 1 - Demographic data, presentation, clinical features, management, disease severity, and outcome of all 13 cases.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Demographics													
Age (years)	34	20	25	22	22	28	43	21	20	23	29	25	18
Gender	F	M	M	F	M	F	M	F	M	M	F	M	M
Nationality	Philipino	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi	Saudi
Weight (kgs)	60	71	116	71	73	60	85	81	80	78	120	55	66
Co-morbidities	Mild scoliosis	None	Obesity	None	None	None	Smoker/ diabetic	None	Smoker	None	Obesity/ asthma	Gilbert syndrome	Bronchial asthma
Presentation (year 2024)													
Possible source	Source-1	Source-1	Source-1	Source-1	Source-1	Source-2	Source-1	Source-2	Random	Random	Random	Source-2	Random
Date of exposure	April 14	April 21	April 23	April 25	April 25	April 24	April 25	April 26	April 30	April 30	April 30	April 30	May 4
Onset of symptoms	April 17	April 22	April 24	April 25	April 26	April 25	April 26	April 27	April 30	May 1	May 1	May 2	May 4
ER presentation	April 18	April 23	April 24	April 26	April 27	April 28	April 28	April 29	April 30	May 1	May 1	May 2	May 5
RRT activation	April 20	April 23	April 24	April 26	None	April 28	April 28	April 29	April 30	May 1	May 1	May 2	May 5
Clinical features													
Dyspghagia	✔	✔		✔	✔	✔	✔		✔	✔	✔	✔	✔
Visual symptoms*				✔		✔	✔	✔	✔	✔	✔	✔	✔
Speech symptoms	✔	✔	✔			✔	✔		✔			✔	
UL weakness	✔	✔		✔		✔			✔	✔	✔	✔	✔
LL weakness	✔			✔					✔	✔	✔	✔	✔
Respiratory symptoms		✔	✔	✔	✔	✔		✔	✔				
GI symptoms	✔				✔		✔		✔	✔	✔	✔	✔
Headach				✔	✔			✔					
Dizziness		✔		✔						✔	✔		✔
Days from presentation to diagnosis	7	3	4	0	0	0	0	0	0	0	0	0	0
Differential diagnosis	GBS	MG/GBS	MG				GBS			GBS	GBS		
IVIG													
IVIG given	✔	✔	✔	✔		✔	✔	✔					
Improvement after IVIG	✔							✔					
Antitoxin													
Days from presentation to antitoxic	7	3	4	0	0	0	0	0	0	0	1	0	0
Improvement after antitoxin	✔		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Adverse reactions to antitoxin	None	None	None	None	None	None	None	None	None	None	None	None	None
3,4-DAP													
Days from presentation to 3,4-DAP	7	3	4	1	None	0	0	0	0	0	1	0	0
Improvement after 3,4-DAP	✔		✔	✔			✔	✔	✔	✔	✔	✔	✔
Adverse reactions to 3,4-DAP	None	HTN	Tachycardia/ HTN	None	-	None	None	None	None	None	None	None	None
Severity and outcome													
MV		✔											
NIV							✔						
HFNC			✔				✔						
ICU LOS (days)	5	Still in ICU	9	9	0	8	2	3	2	4	3	2	2
Discharged	✔	Still in ICU	✔	✔	✔	✔	✔	✔	✔	In rehab	✔	✔	✔
Hospital LOS (days)	19	Still in ICU	13	10	2	10	6	6	2	In rehab	4	3	2

*Visual symptoms include: ptosis, double vision and blurring of vision. M: male, F: female, ER: emergency room, RRT: rapid response team, UL: upper limb, LL: lower limb, GI: gastrointestinal, GBS: Guillain-Barré syndrome, MG: myasthenia gravis, IVIG: intravenous immunoglobulin, 3,4-DAP: 3,4-diaminopyridine, HTN: hypertension, MV: mechanical ventilation, NIV: non-invasive ventilation, HFNC: high flow nasal cannula, ICU: intensive care unit, LOS: length of stay, rehab: rehabilitation

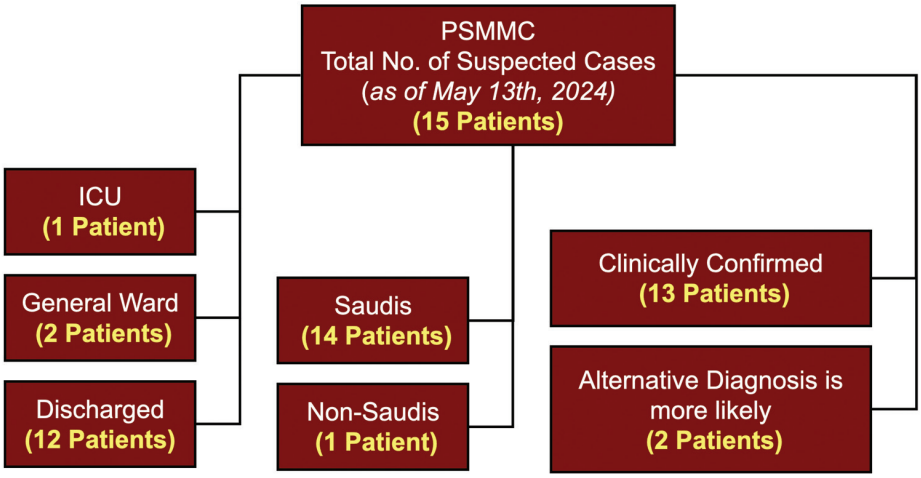

Figure 3 - Statistics of cases in Prince Sultan Military Medical City, Riyadh, Saudi Arabia, as of May 13, 2024. PSMMC: Prince Sultan Military Medical City, No.: number, ICU: intensive care unit

botulism based on the clinical criteria, epidemiological data, and the response to specific therapy. Blood and feces from all patients were sent for toxin detection in the central laboratory while management was ongoing. The Public Health Authority in Riyadh, Saudi Arabia, issued guidelines for foodbrone botulism on April 27th, 2024, version 1.2, in response to this outbreak and the case definitions are introduced. In this document, a suspected case is a clinically compatible case with an epidemiological link (namely, ingestion of a suspect food within the previous 48 hours). On the other hand, a confirmed case is a clinically compatible case that is laboratory confirmed or that occurs among persons who ate the same food as persons who have laboratory-confirmed botulism. Similarly, the Saudi MOH published online guidelines for the diagnosis and management of botulism.

The incubation period in all 13 cases is short, ranging from several hours to 48 hours. Additionally, a canned food additive, like pickles or sauce, could be the culprit rather than the beef but that is still to be confirmed by MOH. The clinical presentation of all 13 cases was very similar and involves mainly the cranial nerves as the initial symptom followed by GI and upper limb symptoms. Fewer patients had lower limb and respiratory symptoms.

The only specific treatment for botulism, in addition to supportive care, is the botulinum antitoxin which should be given as soon as the disease is suspected. If the antitoxin is given within 48 hours and, preferably, with 24 hours of symptoms, it can stop the progression of the disease. It, however, will not reverse any existing weakness.[1,4] The antitoxin simply acts by binding the circulating botulinum toxin that is not yet bound to the presynaptic receptors to form a complex that is then cleared from the patient's system.[5]

Botulinum antitoxin is given intravenously after diluting the 20 ml vial in 200 ml of isotonic saline (1:10). Then it is infused initially at a rate of 0.5 ml/min for 30 minutes and, if no unwanted reactions noted, the rate is increase to 1 ml/min for another 30 minutes, then 2 ml/min until it is completed. Most of the patients in this series reported subjective improvement following receiving the antitoxin. Additionally, all our patients got better in few days following the antitoxin, and were discharged home.

Adverse reactions to the antitoxin are uncommon and are usually related to allergic reactions, mostly skin allergy, headache, and GI symptoms.[1] None of our patients reported or noted to have any adverse reaction.

3,4-Diaminopyridine modifies the function of certain electrolyte channels in the cell membranes that results in increase in presynaptic calcium influx and an improvement in acetylcholine release, enhancing muscle function.[6] It has been classically used for symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS).[6,7] It has been tried first in 1983, then an initial publication of effectiveness in such syndrome in 1989.[8-10] These studies and few others showed improvement in the motor and autonomic symptoms related to LEMS.[11,12]

3,4-Diaminopyridine was given to 12 out of the 13 cases, and it was remarkable that most patients reported improvement in symptoms after taking the tablets. Although, it will never be possible to distinguish if that subjective improvement is related to 3,4-DAP, the antitoxin or other factors, but this observation opens the door wide for further research to prove or disprove such observation. Additionally, there should be more objective measures to quantify the improvement

Table 2 - Clinical, management, and outcome data of study cases.

Variables	n (%)
Total number of patients	13 (100)
Demographics	
Age (<30 years)	11 (85.0)
Male	8 (62.0)
Female	5 (38.0)
Co-morbidities	6 (46.0)
Source of poisoning	
Source-1	6 (46.0)
Source-2	3 (23.0)
Random source	4 (31.0)
Clinical presentation	
Incubation period	Few hours - 48 hours
Dyspghagia	11 (85.0)
Visual symptoms	9 (69.0)
Speech symptoms	7 (54.0)
UL weakness	9 (69.0)
LL weakness	7 (54.0)
Respiratory symptoms	7 (54.0)
GI symptoms	8 (62.0)
Headach	3 (23.0)
Dizziness	5 (38.0)
IVIG	
Patients received IVIG	7 (54.0)
Improvement after IVIG	2 (29.0)
Antitoxin	
Patients received antitoxin	13 (100)
Improvement after antitoxin	12 (92.0)
Adverse reactions to antitoxin	0 (0.0)
3,4-DAP	
Patients received 3,4-DAP	12 (92.0)
Improvement after 3,4-DAP	10 (83.0)
Adverse reactions to 3,4-DAP	2 (17.0)
Disease severity and outcome	
Patients required ICU care	12 (92.0)
Patient required MV	1 (8.0)
Patient required NIV	1 (8.0)
Patient required HFNC	2 (15.0)
Patients discharged home	11 (85.0)
ICU LOS*	4 (2-9) days
Hospital LOS†	7 (2-19) days

Values are presented as numbers and percentages (%), average (minimum-maximum). *Excluding a patient who is still in ICU. †Excluding the 2 patients who are still in the hospital. UL: upper limb, LL: lower limb, GI: gastrointestinal, IVIG: intravenous immunoglobulin, 3,4-DAP: 3,4-diaminopyridine, MV: mechanical ventilation, NIV: non-invasive ventilation, HFNC: high flow nasal cannula, LOS: length of stay

noted. The patients who reported improvement after receiving 3,4-DAP are those who did not have more severe respiratory symptoms, suggesting that it may be more useful if used early in the course of the disease.

This medication is given as oral tablets, at a dose of 10 mg twice daily to 4 times a day (maximum daily dose of 100 mg). The side effects of 3,4-DAP are usually mild and most often consist of paresthesia, but epileptic seizures and arrhythmias were reported when higher doses are used.[13] The frequency and nature of these side effects encouraged us to use this medication in these patients. All 12 patients who required ICU care received 3,4-DAP and only 2 developed transient hypertension or tachycardia that may be linked to it.

Patient-2 is still mechanically ventilated and it seems that there is no much improvement in the condition despite the antitoxin and 3,4-DAP. This could be because botulism was considered relatively late and, hence, received the treatment late. Additionally, the patient may have ingested a considerable dose of the toxin compared to others.

Study limitations. This case series is small and should be interpreted in that context. Although we may have found some subjective benefits of using 3,4-DAP in patients who received it, a larger, prospective trial should be carried out to confirm that.

In conclusion, an uncommon condition like botulism may cause outbreaks that could stretch the health care system to the limits. If not treated early, it may cause significant mortality and morbidity. The take home message of this study is to try to identify botulism early, even before the outbreak is evident. Treatment with botulinum antitoxic must be started as soon as possible for better results. Additionally, 3,4-DAP effectiveness in facilitating the resolution of botulism symptoms should be studied in randomized control trials. Objective measures to quantify response should be developed as well. Until that is accomplished, we suggest considering the use of 3,4-DAP in patients with botulism particularly early in the course of the disease as it is potentially useful and is generally safe.

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