Our experience in the treatment of botulism

Naše iskustvo u lečenju botulizma

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Abstract

Introduction. Botulism is a neuro-intoxication caused by a toxin secreted by Clostridium botulinum. Due to extremely high toxicity and lethality, this toxin can be used as an agent in a biological warfare. Case report. We presented six patients, mean age 28.8 years, who ate canned food and in whom the diagnosis of disease was made based on the typical clinical picture. Predominant symptoms were blurred vision, double vision (diplopia), dry mouth and constipation which were present in all patients. The patient whose disease was recognized only after 23 days and who did not receive the antitoxin serum underwent the longest hospital treatment. All the patients received antibiotics and 4 patients received antitoxin. Neostigmine and enemas were used for the treatment of the disorder of intestinal motility and constipation.

Conclusion. The diagnosis of botulism was made based on afebrility, preserved states of consciousness, double vision, dry mouth and history data on consumption of suspicious food. Polyvalent serum antitoxin should be applied as soon as possible because it reduces the occurrence of complications, length of hospital stay and mortality rate.

Key words: botulism; decontamination; botulinum antitoxin; treatment outcome; bioterrorism.

Apstrakt


Ključne reči: botulizam; dekontaminacija; botulin, antitoksin; lečenje, ishod; bioterrorizam.
Botulism transmitted by food occurs after consuming contaminated food in which the toxin is produced; in the other two forms, C. botulinum produces a neurotoxin in vivo, in the infected tissue or in the colon. Today, it is known that the botulinum neurotoxin on peripheral nerve endings binds to two receptors on neurons by its synaptic vesicle R subdomain with a low affinity for the ganglioside and high for a synaptic vesicle protein known as a synaptic vesicle (SV2A) and SV2B and synaptotagmin II (Syt II). After that, a toxin that is bound to the receptor by endocytosis enters the cell,\(^5,6\) and leads to the blockade of acetylcholine release at the level of neuromuscular synapse, which results in the appearance of paralysis.

Infant botulism occurs most often in infants younger than 6 months\(^3\). Since botulinum is one of the strongest toxins, it is considered that 1 ng/kg is lethal to humans, while 200 g in the form of crystalline is enough to kill all of the humanity. It can be used in bio-warfare\(^7,8\) and it belongs to class A of biological agents.\(^9,10\) It can be used by spraying into the air or injecting into food.

Since botulism is a rare disease, early recognition of clinical symptoms is highly important for serum anti botulinum application. Furthermore, it is also necessary to report the disease and epidemiological treatment of each case.

**Case report**

We reported 6 patients diagnosed with botulism, who were treated during the period of ten years (from January 2004 to January 2014) in the Clinic for Infectious Diseases, the Clinical Center Niš, Serbia. The diagnosis of botulism was made based on the clinical picture and the epidemiological surveys, and according to the disease evolution and further paraclinical tests, differential diagnostic capabilities (CDC recommendations - USA) were excluded\(^11\).

**Case 1**

A 44-year-old patient, an electrical engineer, presented with nausea, vomiting and watery excrement. The disease occurred in November 2007. Two days after the initial symptoms, in the evening hours, diplopia, dryness of the mouth, fatigue, difficulty in swallowing and speaking occurred. He gave the epidemiological data that he had eaten a can of squid seven days before the onset of symptoms and smoked meat the day before the onset of the symptoms. He was hospitalized three days after the illness had occurred, with signs of dryness of mucous membranes and mydriasis. Lung X-ray showed vague contours of the left dome of the diaphragm, which may correspond to the left, basal pulmonary infiltrate. The control lung X-ray done five days later was normal. The test of neuromuscular transmission was also performed and it showed a slight increase, up to 10%, on the system nervus medianus-musculus abducens poll left of evoked muscular responses I-IV, while there was no increase in the amplitude of evoked muscular responses in other tested systems. During the hospitalization for constipation, deep enema with sodium chloride solution 0.9% (NaCl) was also applied to the patient on two occasions. He was treated with anti botulinum serum (one dose of commercial serum, consisting of 750 IU of antitoxin A, 500 IU antitoxin B and 50 IU antitoxin E.), neostigmine (0.5 mg im for 7 days) and metronidazole 500 mg/8 h for 10 days. The patient was cured and discharged after fourteen days.

**Case 2**

A 26-year-old male patient, a student, presented with vomiting and constipation in mid-July 2008. He gave an indication that the previous day he had eaten “a can of meat.” Diplopia, dryness of mucous membranes in the mouth and difficulties swallowing and speaking occurred two days after consuming the suspected food. On admission, four days after the onset of symptoms, mydriatic pupils, non-responsive to light, dehydration signs, left tonsil arch elevation and speech difficulty were noticed. He was treated with neostigmine 0.5 mg im for 7 days, lactulose and penicillin G, 10 million IU daily for 10 days. During hospitalization, despite the application of lactulose and deep enemas with 0.9% NaCl, the constipation persisted for few days after discharge.

**Case 3**

A 19-year-old female patient, a student, presented with nausea and vomiting in October 2009, the day after she consumed pate of unusual taste and sardines. The next day, blurred vision, dryness of oral mucous membranes, sore throat and difficult swallowing occurred. She was referred to a neurologist who prescribed her medication for “circulation”. She was hospitalized four days after the onset of clinical symptoms, with signs of adynamia, dehydration, mydriatic pupils which poorly responded to light and accommodation, as well as with decreased strength. On admission, laboratory analysis of blood verified leukocytosis 11.6 \(\times 10^9/L\) [normal range (nr) 4–10.5 \(\times 10^9/L\)], with dominance of polymorphonuclears 80% (nr 50–70%), C-reactive protein (CRP) 45.3 (nr less than 3 my/L), fibrinogen 7.4 g/L (nr 1.5–3 g/L (she was also diagnosed with concomitant urinary tract infection for which she was treated with ceftriaxone). During hospitalization, the enema was applied on several occasions and stool became regular 15 days after the treatment. She was treated with neostigmine 0.5 mg im for 7 days, penicillin G, 10 million IU daily for 10 days, and received the anti botulinum serum (one dose of commercial serum, consisting of 750 IU of antitoxin A, 500 IU antitoxin B and 50 IU antitoxin E). Clinically rehabilitated, she was discharged from the clinic after 17 days.

**Case 4**

An 11-year-old patient, a pupil, presented with nausea and vomiting in June 2010, the day after he consumed pate in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”. Vomiting and constipation in mid-July 2008. He gave indication that the previous day he had eaten “a can of meat”.

swallowing, hoarseness. He was afebrile during the whole course of illness. He was hospitalized on the fifth day of the illness and on admission he had eyelid ptosis, mydriasis, dryness of mucous membranes. The patient was adynamic and arrived in a wheelchair. The patient had elevated sedimentation 80 mm/h (nr 0–22 mm/h), with leukopenia 4.2 × 10^9/L, normal findings of leukocytes formulas and CRP 17.3 g/L. He was treated with neostigmine 0.5 mg im for 7 days, ceftriaxone 2.0 g daily for 10 days, and has received the anti botulinum serum (one dose of commercial serum, consisting of 750 IU of antitoxin A, 500 IU antitoxin B and 50 IU antitoxin E). The problem of constipation was solved by enema (0.9% NaCl) which was performed on the fourth day of hospitalization, and thereafter the patient had regular excretion of feces. The patient was cured and released after eleven days of hospital treatment.

Case 5

A 45-year-old patient, a journalist, presented with nausea, pain in bowels, vomiting and mild diarrhea in mid-July 2010, a day after he had eaten pate in the casing of dubious quality. Dryness of the palms and soles, difficulties in swallowing, “blurred vision”, hoarseness and constipation occurred after two days. His chosen doctor treated him with metoclopramide hydrochloride and he was also treated by a neurologist and ophthalmologist. He was admitted six days after the first symptoms appeared and on admission, he had anisocoria, dysphagia, dysphonia, adynamia, dehydration, and tachycardia 98 beats/ min. He was treated with neostigmine 0.5 mg im for 7 days, metronidazole 500 mg/8 h for 10 days and the anti botulinum serum (one dose of commercial serum, consisting of 750 IU of antitoxin A, 500 IU antitoxin B and 50 IU antitoxin E.). Due to constipation, enema with 0.9% NaCl was done only on the day of admission and later he had regular stools. Clinically cured, he was released after fourteen days.

Case 6

A 31-year-old patient, an electrical engineer, presented with nausea, belching, vomiting and 5–6 watery excrements in February 2013. After 72 h he developed blurry vision regardless of distance, difficult swallowing and constipation, tiredness and was unstable in standing position. During the treatment, he passed stool on the third day and after that his stool was regular so there was no need for using enemas. He was treated with penicillin G, 10 million IU daily for 10 days, neostigmine 0.5 mg im for 7 days and infusion solutions with vitamins B and C. The patient was cured and released after thirteen days of treatment. Table 1 summarizes the different symptoms and signs in patients with botulism.

Discussion

Botulism can occur regardless of age. Sobel et al. showed that in a sample of 263 patients, the average age was 48 years. Leclair et al. tested a sample of 205 patients from Canada during a period 1985–2005 and showed that mean age was 45 years (3–83 years), with 48.4%. They also stated that the prevalence of type E botulinum toxin was 86.2%. These findings are consistent with our case series. The patients hospitalized in our Clinic were aged from 11 to 45 years, with a mean age of 28.8 years. Four patients were male and two were female.

### Table 1

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>nausea</td>
<td>6 (100)</td>
</tr>
<tr>
<td>vomiting</td>
<td>6 (100)</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td></td>
</tr>
<tr>
<td>constipation</td>
<td>6 (100)</td>
</tr>
<tr>
<td>dryness of mouth</td>
<td>6 (100)</td>
</tr>
<tr>
<td>dryness of palms: soles</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Neurological system</td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td>3 (50)</td>
</tr>
<tr>
<td>blurred vision</td>
<td>6 (100)</td>
</tr>
<tr>
<td>diplopia</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>eyelid ptosis</td>
<td>1 (16.6)</td>
</tr>
<tr>
<td>hoarsness</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>difficulty swallowing</td>
<td>6 (100)</td>
</tr>
<tr>
<td>general weakness</td>
<td>4 (66.6)</td>
</tr>
</tbody>
</table>

Based on epidemiological surveys, the most likely route of infection in four patients was the pate, in one patient the luncheon meat, and in one it was most likely dried meat. Therefore, the route of infection in all cases was alimentary. It was not possible to prove the presence of *C. botulinum* toxins in suspicious food samples, considering that they had not been preserved. Apart from the patients, no one else had consumed the suspected food so there was no control group.

Besides the most frequently mentioned antigenic types that cause botulism, Bouvet et al. described the case of an 83 year-old-person with clinical signs of severe sepsis in whom *C. botulinum* type III, which had a “mosaic structure” of genetic parts of C and D types, was isolated from the blood cultures.

The incubation period ranged from 24 h to four days. Arnon et al. showed that the first symptoms, in the form of descending symmetric paralysis, bulbar paralysis, diplopia, dysarthria, dysphagia and dysphonia occur 12 to 72 h after exposure. The youngest patient was 11 years old and had the shortest incubation period because he stated that 30 min after eating pate, he felt nauseated and vomited abundantly, and the next day he got the neurological symptoms.

The most predominant symptom, which aroused general practitioner’s suspicion of botulism, was a disturbed vision. All patients had blurred vision, double vision and could not read. In all cases the dryness of mouth, difficulties in swallowing and speaking were recorded. With the youngest patient, in addition to mydriasis, the ptosis of the eyelids was registered. Some authors state that the clinical picture is characterized by the triad – symmetric descendent paralysis and bulbar paralysis, afebrility and preserved sensorium. Aurora et al. give an overview of the case of a 35-year-old patient from India, who, 4 days after consuming food, deve-

developed eyelid ptosis, blurred vision, difficult swallowing, pro-
gressive weakness of the lower limbs and fasciculation of the
muscles of the whole body, which is rarely seen.

Describing the occurrence of 30 cases of patients suf-
fering from botulism poisoning after eating in a restaurant in El
Paso, Texas, Angulo et al. 19 said that in 18 of them the diag-
nosis was confirmed, with 5 it was likely, and in 2 cases it
was suspicious. The most common symptoms were fatigue,
diplopia, blurred vision and dizziness. They specifically po-
t out two cases with the asymptomatic clinical picture. With
one, the diagnosis was made on the basis of positive
coprocultures, and in the other the findings of
electromyography were specific. Sobel 20 pointed out that in
a case of an epidemic, all patients did not have the same cli-
nical picture because the toxin was not equally distributed in
all contaminated groceries.

Khakshoor et al. 21 described the case of a 37-year-old
Iraqi who had a binocular horizontal diplopia as the only sign
of the disease. Three days later, the patient began to vomit,
and two days later he developed other symptomatology of
botulism.

As it can be seen from the mentioned cases, the diagno-
stic wanderings are frequent, whether the patients are treated
with suspicion of other diseases or whether the referral to vi-
rologist was belated, even three weeks after the onset of the
symptoms.

Vossen et al. 22 pointed out the rare frequency of the di-
sese and the importance of early recognition of the clinical
picture indicates. They described two cases of botulism in
Vienna that were diagnosed after a period of 21 years in
which there was no botulism. Besides the selected physician,
an ophthalmologist, laryngologist, and gastroenterologist
were consulted and on the eighth day of the disease, when a
neuro-ophthalmologist was consulted, an infectologist was
included and the disease was diagnosed. Early diagnosis is
needed for timely application of serum which is the first 36
h. Sobel 20 points out that it would be ideal to apply the anti
botulinum serum in the first 24 h of the symptom onset.

Kotan et al. 23 state that in addition to the characteristic
clinical picture, it is also possible to use electromy-
neurography (EMNG) for the purpose of diagnosis. They
presented the case of a 43-year-old female patient who de-
veloped neurological disorders and indicated the specific find-
ings of EMNG in botulism. The response to repeated stimu-
lation of the ulnar nerve with low-frequency (3 Hz) is
lowered, while at the repeated stimulation with high
frequencies (10–50 Hz), the response is facilitated 23, 24.

In two patients the therapy did not include the serum
anti botulinum, because one of them appeared 23 days from
the onset of symptoms and the other after 5 days. Both pati-
ents were treated by antibiotics, neostigmine, lactulose, and
infusion of electrolytes and vitamins. Lonati et al. 25 presen-
ted the case of a nine–month- old infant with a severe clini-
cal picture of botulism who, in addition to serum anti buli-
um 250 mL / 25 mL / h, was also orally given 5 g activated
charcoal through a nasogastric tube and prostigmine 0.05 i.v.
mg/kg. The same group of authors believes that the applica-
tion of prostigmine inhibits the enzymatic degradation of
acetylcholine and therefore may be useful in preventing ileus 26.

Other four patients were given trivalent serum anti botuli-
num - Botulinum Antitoxin Behring® from the company
Novartis. The serum contains horse proteins but since the pa-
tients were not previously treated with sera of animal ori-
gin, the premedication was not carried out. Antibotulinum se-
rum was applied in the form of a slow i.v. infusion of 250
mL, and then sequenced with another 250 mL. After 4–6 h
another 250 mL of the serum was infused. There was no re-
action in any of the patients. With the use of neostigmine, the
patients were also given antibiotics, lactulose, and other
symptomatic therapy. Robinson et al. 27 believe that early use
of serum anti botulinum prevents the progression of paralysis
but it does not cure it. A group of authors believes that there
are certain doubts about the application of serum anti botuli-
um since it can cause anaphylaxis, and as additional treat-
ment options, they listed corticosteroids, plasmapheresis, and
implementation of immunoglobulins 18. Tacket et al. 28 de-
scribe the evaluation of the effect of using trivalent horse se-
rum in 132 patients with clinical signs of botulism and note
that it has a positive effect on the survival and shortens the
course of the disease.

Some authors believe that passively applied animal se-
rum only leads to neutralization of toxins in circulation by
binding antitoxins to receptors of neurons, where it cannot
directly inhibit the proteolytic activity of toxin which entered
the cell. Humanized monoclonal antibodies bind and block
the action of zinc metalloprotease intracellularly. In that case,
botulinum neurotoxin cannot cause specific and direct adver-
ses effects. Accordingly, humanized monoclonal antibodies
should be immunotherapeutic medicine for botulism 29.

Lonati et al. 25 say that Dr. Zamani recommends the ste-
rilization of hose by using sorbitol and does not recommend
the use of magnesium salts as they can lead to a deteriora-
tion of neuromuscular blockades.

A group of Japanese authors described the case of a 69-
year-old married couple suffering from severe forms of botu-
lim after eating vacuum packed food. They tested the pre-

cence of toxin and Clostridium in the feces and toxin in the
serum. For epidemiological reasons, it is essential that, at the
beginning of their disease, Clostridium in feces was isolated
in both patients and toxin was detected in serum and feces.
After three months, the toxin was not detected in the serum,
in one patient it was detected in the feces, and in both pati-
ents Clostridium was isolated in the feces 30.

The role of antibiotics in the treatment of botulism rema-
ins unclear but penicillin G has been recommended to treat
wound botulism. Any other antibiotics that treat Clostridium
species, such as cefalosporins or metronidazole could also be
administered. Antibiotics are useful in wound botulism, but
they have no role in foodborne botulism. Antibiotics are also
useful in the treatment of secondary infections. In infant botu-
lim, antibiotics are used only to treat secondary infections be-
cause lysis of intraluminal C. botulinum may increase the
amount of toxin available for absorption 31.

The length of hospitalization ranged from 11 to 20 days,
noting that two patients were treated for 14 days, and one 13

and 17 days. The longest treatment had the patient who was admitted 21 days after the first symptoms, which were not recognized on time and he had not received anti-botulinum serum. All patients were cured without sequelae.

**Conclusion**

Botulism is a neurointoxication which is characterized by afebrility, the appearance of visual disturbances, difficult swallowing, dryness of mucous membranes in the mouth, constipation and preserved sensorium. The main clinical symptoms that aroused the doctor’s suspicion of the disease are diplopia and visual disturbances. *Clostridium botulinum* can be used in bioterrorism as a biological poison and, therefore, there is an imperative need to report every case of suspicion of the disease. Treatment of patients must be carried out in intensive care units. Anti botulinum serum should be applied as soon as possible because it reduces the occurrence of complications, length of hospital stay and mortality rate, but the problem is the fact that, in any case when the serum was required it could not have been obtained in the country and had to be commissioned from abroad.

**References**


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