A CASE OF BOTULISM (CASE REPORT)

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Abstract. Data on rising number of cases of food botulism in Ukraine is discussed in the article. As a clinical example, unusual case of food-borne botulism of a patient in Kharkiv is described. Peculiarity of the case is a development of symptoms of the disease in patients with compromised psychoneurological background and exacerbation of chronic pancreatitis so the clinical presentation mimicked other acute progressive neurological disorders. Differential diagnostics is presented. Experience and effectiveness of Heptavalent Botulism Antitoxin (HBAT), which was used for the first time in our hospital for treatment of botulism is discussed.

Key words: *symptoms, treatment, heptavalent, botulism, antitoxin.*

Introduction. Botulism is an uncommon paralytic disease caused by neurotoxins produced by Clostridium Botulinum (toxin types A, B, E, F, and H), and rarely, by botulinum-producing strains of *Clostridium butyricum* (type E toxin), *Clostridium baratii* (type F toxin) and *Clostridium argentinense* (type G toxin). Spores, formed by strains of *C. botulinum* Group I, are highly resistant to heat, and "Botulinum cook" at 121°C for 3 minutes given to low acid canned foods has been designed to inactivate these spores [1]. The number of neurotoxin genes present in the genome, and neurotoxins actually formed by strains of *C. botulinum* Group I is variable, with strains possessing from one to three neurotoxin genes, and forming one to three different neurotoxins. There are five forms of botulism, characterised by the mode of acquisition: infant botulism, wound botulism, foodborne botulism, adult enteric infectious botulism, and inhalational botulism [2, 3]. The germination and subsequent production of the toxin in foods only occurs under anaerobic, low-salt and low-acid conditions. Both canning and fermentation of food create anaerobic conditions that facilitate the growth of *C. botulinum* spores and contaminated home- or commercially-canned foods which typically include fish, meat and vegetables [4].

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Over the last four years, Ukraine faced an outbreak of botulism. From the beginning of 2018, 80 cases have been recorded, 9 of them were fatal. Cases of deaths from botulism that occurred in 2018 year in Kyiv, Poltava, Sumy, Kharkiv and Cherkasy regions were associated with the use of dried fish of industrial production. In other cases, people died after consuming dried fish of domestic production, as well as homemade stew and salted-smoked fish. Despite of growing number of cases of the disease practicing physicians still may face difficulties in proper diagnosis. Usually, the diagnosis should be suspected on clinical grounds in the context of an appropriate history. Diseases, most frequently confused with botulism are those that produce generalized weakness, neurological symptoms or even diarrhoeal diseases. Proper differential diagnosis of botulism from other diseases is essential for early initiation of specific treatment or proper direction of a patient to specialized hospital. Botulism is relatively easy to consider in patients who are afebrile and previously mentally intact but suddenly develop symmetric descending paralysis without sensory abnormalities. But cases of the disease in patients with compromised psycho – neurological background is always a big challenge so the clinical presentation can mimic other acute progressive neurological disorders.

Clinical case. Our study involved assessment of a clinical case of botulism to illustrate a diagnostic problem. A 22-year-old female

presented with moderate spasmodic colics in the left paraumbilical area, nausea, vomiting, dizziness, bitterness and dryness in the mouth, double vision and expressed weakness. With suspected acute pancreatitis she was admitted to surgical department. After diagnostic procedures exacerbation of chronic pancreatitis was confirmed. Urgent laboratory examination showed an increased level of serum amylase to 40.1 mg.hr/ml and neutrophilic leucocytosis which also confirmed the diagnosis.

But additionally to the signs of pancreatitis unusual symptoms were revealed. She developed diplopia, severe dryness in the mouth, feeling of "clod" in her throat, choking in process of drinking of water, constant moderate headache and irritability. Therefore, she was examined by a neurologist. Neurological examination showed horizontal nystagmus, with no signs of central nervous system damage, bilateral ophthalmoplegia, full symmetrical paralytic mydriasis, lower motor neuron facial weakness, dysarthria, dysphonia and glossal paresis. She had subtle distal weakness in both hands. Reflexes were retained. The patient remained alert and afebrile. She was also tachypnoic to 28/min. The oxygen saturation was 98% while breathing ambient air.

According to past history the patient was under supervision of psychoneurologist for about ten years with some disorders. Six years before she was admitted to psychoneurological hospital for a long treatment. Previously the patient repeatedly imitated suicide through cutting of her peripheral veins. Patient also smoked about 20 cigarettes a day and quite often drank alcoholic drinks. Epidemiological data suggested that about four hours before disease onset she ate dried fish (roach) which she bought in the nearest market. No family members consumed this food so they remained healthy at the moment of patient examination.

According to all data the diagnosis of botulism was suspected. The patient was urgently transferred to Kharkiv Regional Hospital of Infectious Diseases. On examination, the patient appeared anxious, with dry mucous membranes. The hematocrit, platelet count, erythrocyte sedimentation rate, and levels of hemoglobin were normal, as were tests of renal and liver function. But there were disturbances of acid-base balance as decompensated respiratory acidosis, namely ðÍ 7.193, ðÎ $_2$ 145.3 mm Hg, ðÑÎ $_2$ 70.8 mmHg. Follow-up electrocardiography did not show any abnormalities.

Within four hours her condition deteriorated rapidly; she developed respiratory failure, SpO_2 level fell till 80% and required intubation and ventilation. A nasogastric tube was inserted and formula feedings were administered. Her condition continued to worsen and she developed acute flaccid symmetrical paralysis. Psychomotor excitement was accompanied probably due to accompanied chronic psychoneurological disease.

On the second day of disease, the day of admission, the patient was treated with Heptavalent Botulism Antitoxin (A, B, C, D, E, F, G) and required ten days of mechanical ventilation and 20 days of intensive care support. Blood, stool and gastric washings were cultured, but no *Clostridium* species were isolated. In this case, the mouse neutralization test was used to detect toxin in serum and an aqueous extract of stool. *C. botulinum* toxin type A was confirmed. On the next day her fever was accompanied by auscultatory symptoms, namely reduction of pulmonary sounds and moist rales in her left subscapular zone suggested pneumonia in the left lower lobe which was confirmed by radiography of the chest on the 7th day of the disease. A course of antibacterial treatment started with ceftriaxone 2.0 g twice a day intravenously in combination with levomycetin 500 mg 4 times a day. But in progress of the disease febrile condition was accompanied by leucocytosis 10.8×10^9, ESR increased to 34 mm/hr and neutrophilic shift. Culture from endotracheal tube showed growth of *Acinetobacter lwoffii* and *Candida spp*. According to the data antibacterial treatment was changed to metronidazole 1.5 g daily dose in combination with meropenem 6 g as a daily dose.

In the process of treatment infiltration regressed to 22nd day of her disease. The patient also was provided symptomatic treatment to regain water – electrolyte balance and neuromuscular transmission.

The patient's motor function showed signs of paralysis, absence of spontaneous breathing, controlled with artificial respiration in VCV regimen in combination with medication sleep because of continued encephalopathy of mixed origin. The patient returned to spontaneous breathing on the 11th day of disease. There was enteroparesis with absence of intestinal peristalsis sounds and spontaneous defecation. Follow-up neurological examination revealed stable divergent strabismus of both eyes, expressed bilateral ptosis, diplopia when looking from side to side persisted, decreased deep reflexes in lower limbs. Muscular paresis was severe till the 10th day of disease and Babinsky sign was present on both legs. Follow-up neurological status gradually

improved to the 28th day of disease. The patient still presented with mouth dryness and persistent constipation. One month after the onset of her symptoms, she was discharged home.

Discussion. Although classical botulism is a quite rare disease in developed countries, in some regions there are increased number of cases, first of all with specific food habits and privileges of local population. In European countries there are only sporadic cases of the disease, in USA there are about 110 cases of botulism a year, most of them are cases of infant botulism [5]. In Ukraine some of such factors are wide consumption of homemade canned meat and dry fish, quite often bought in uncontrolled markets, without thermal treatment. According to reports from different countries same clinical data typically appear within 12 to 36 hours after the consumption of the tinned or dry food. Anorexia, nausea and vomiting (77.4%), abdominal pain (54.8%) and blurred vision with diplopia (48.4%) are the most usual clinical symptoms followed by the progressive muscular weakness of the face, neck, trunk, and limbs as well as by respiratory insufficiency primarily due to paresis of diaphragm [6–8]. About 70% of the patients have three of five symptoms as nausea and vomiting followed by meteorism and stable constipation, dysphagia, diplopia, and a group of ophtalmoplegic symptoms eyelid ptosis, more or less expressed paralytic mydriasis, blurred vision with sense of "net" or "mist", which are the combination of neurological and gastrointestinal symptoms. Typically differential diagnosis includes Guillain-Barré syndrome, Miller-Fisher syndrome, stroke, chemical intoxication and staphylococcal food poisoning. Suspected drug and alcohol abuse may occasionally prolong the time for diagnosis to be made [9]. In the presented case symptoms of exacerbation of chronic pancreatitis and some psychoneurological disease, unclear due to lack of history data mimicking clinical symptoms resulted in some delay before proper diagnosis was made and treatment started. Botulism is a life-threatening disease, but rapid laboratory diagnosis, required for successful therapy is still not always available in practical clinical medicine. Of these, detection of toxin in the patient's serum and/or feces remains the standard method [10]. Detection of C. botulinum in patient samples, such as feces, gastric and intestinal contents, and wound swabs and tissues, supports the diagnosis but should not exclusively be considered pathognomonic of the disease [11]. So the mouse lethality assay (neutralization test) has remained the standard test for the detection of botulinum neurotoxins, as in the case. According to time of getting the results specific treatment should not be delayed and started empirically in most of our cases based on experience of the specialist. For the last two years we for the first time in Ukraine used Heptavalent Botulism Antitoxin (HBAT) (Emergent BioSolutions, Canada), which is a mixture of immune globulin G fragments against botulinum neurotoxins of types A, B, C, D, E, F, G, which had the Fc portion cleaved off, leaving the F(ab')2 and Fab portions. This process renders it less effective in neutralizing toxin than trivalent (against types A, B, and E) botulinum antitoxin (contains whole antibodies – Fab & Fc portions) that is available from local health departments [12].

HBAT is indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxins in adults and pediatric patients. HBAT was approved in 2010 by the CDC and was licensed for commercial marketing by the FDA in 2013. The effectiveness of HBAT is based solely on efficacy studies conducted in animal models of botulism. HBAT was approved in 2010 by the CDC on an investigational basis, and was licensed for commercial marketing by the FDA in 2013. The effectiveness of HBAT was based solely on efficacy studies conducted in animal models of botulism. In two clinical studies cited by Emergent BioSolutions the safety profile of HBAT was proven acceptable when one or two vials of the antitoxin were intravenously delivered to healthy subjects.

The mechanism of action of HBAT is through passive immunization with equine polyclonal antibody fragments against botulinum neurotoxins. In the circulation these antibody fragments bind to free toxins. This prevents the toxins from interacting with ganglioside anchorage sites and protein receptors on the cholinergic nerve endings. In turn this prevents toxins internalization into the target cells. The antibody/antigen complexes are then cleared from the circulation by the organs involved in processing immune complexes. Experimental evidence concerning the amount of circulating antitoxin needed to counteract toxins intoxication is not fully documented. The outcome of treatment depends, as it does with other comparable conditions, largely on the time interval elapsing after the onset of symptoms and antitoxin administration.

In our case the patient with severe complicated food-borne botulism treated with

HBAT successfully recovered and was discharged after one month of treatment. Also the patient had no allergic or other side effects in process of treatment.

Conclusions:

1. Difficulties in diagnosis of food-borne botulism are conditioned by rare incidence of the disease and absence of vigilance of general practitioners. In addition chronic gastrointestinal and psychoneurological diseases can mask clinical symptoms, as in this case.

2. Heptavalent Botulism Antitoxin (A, B, C, D, E, F, G) was used in Ukraine for the first time, and it was proven as an effective method in complex treatment of severe complicated case of food-borne botulism.

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