Chapter 7
Botulism

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7.1 Definition

Botulism is a potentially fatal neuroparalytic syndrome caused by the action of a neurotoxin produced by the bacterium *Clostridium botulinum*. *Clostridium botulinum* is a diverse group of anaerobic gram-positive bacteria that produces spores. The spores are resistant to approximately 100°C for 5 h. These bacteria are ubiquitous and can be easily isolated from the surface of fruit, vegetables, and fish and are present in soil and in marine sediment around the world [1].

Botulism can occur in different forms, which can be distinguished on the basis of the acquisition mode [2]:

- Food botulism: caused by the ingestion of food contaminated with botulinum toxin
- Infant botulism: caused by the ingestion of spores which then colonize the host gastrointestinal tract and release toxin produced in vivo (this can occur, though more rarely, in adults)

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- Wound botulism: infection of a wound by the *Clostridium botulinum* with subsequent in vivo production of the neurotoxin
- Inhalation botulism: linked to inhalation of the toxin in aerosol form, as can happen in cases of bioterrorism
- Iatrogenic botulism: linked to the use of the botulinum toxin for cosmetic purposes

7.2 Pathogenesis

There are eight different types of toxins produced by *C. botulinum*, indicated by the letters A to H. Of these eight types A, B, E, and rarely F, G, and H cause disease in humans. The toxin is composed of a light chain and a heavy chain. Regardless of the route of entry into the body, the toxins spread through the bloodstream and reach the peripheral cholinergic synapses both at the neuromuscular junction and the ganglia level of the autonomic nervous system, where they bind to a specific receptor (synaptotagmin II) localized at the level of presynaptic membrane [3, 4].

The heavy chain binds to the receptor, allowing the light chain to be translocated within the nerve cell by means of an endocytosis mechanism [5]. Once entered into the cell cytoplasm, the toxin inhibits the normal acetylcholine release mechanism at the presynaptic terminal. Restoration of the normal transmission mechanism requires the appearance of new axon terminals and the formation of a new synapse, a process that occurs over approximately 6 months.

Botulinum toxin is the most powerful bacterial toxin and one of the most powerful existing poisons. It is estimated that 1 g of botulinum toxin in aerosol form can kill 1.5 million people.

7.3 Epidemiology

In the United States, an average of 110 cases of botulism is reported per year by the Centers for Disease Control and Prevention (CDC). Infant botulism accounts for about 72%

of the cases, food-related botulism accounts for 25%, and the remaining 3% is due to wound botulism. In cases where botulism is suspected, it is essential to collect a detailed history of the patient in order to search for possible sources of exposure, referring in particular to the preparation of food stored in the home, exposure to other possible food sources, the use of drug injecting, and the use of botulinum toxin for cosmetic purposes.

7.4 Clinical

Botulism generally has an acute onset involving bilateral impairment of the cranial nerves associated with a descending flaccid quadriplegia [6]. In food contamination the symptoms usually occur between 12 and 36 h after ingestion of the toxin. Prodromal gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, and dry mouth can be present. Cranial nerve involvement occurs early and compromises both intrinsic (mydriasis fixed) and extrinsic (paralysis of the III, IV, and VI cranial nerves) ocular mobility which results in blurred vision, ptosis, diplopia, dysphagia, and dysarthria. Facial weakness may also appear. The descending muscle weakness usually progresses to affect the trunk, the upper limbs, and finally the lower limbs up to tetraparesis/flaccid plegia. The involvement of the diaphragmatic muscles can cause respiratory failure requiring intubation. Infant botulism rarely appears with such a dramatic picture as in the adult forms and is typically characterized by hypotonia, weakness, weak cry, and constipation.

Some American CDCs suggest that the following should be considered as core elements of botulism:

- Absence of fever
- Preserved state of consciousness
- Absence of sensory deficits except for blurred vision
- Symmetrical motor deficit
- Normal heart rate or bradycardia and normal blood pressure.

Wound botulism can have different characteristics from food contamination, as there are no gastrointestinal prodromal symptoms, and it may be associated with high fever, the latter probably determined by coinfection of the wound by non-clostridial bacteria species.

7.5 Diagnostic Tests

Clinical suspicion is of fundamental importance in diagnosing botulism.

There are serological tests for detecting the toxin and analysis of vomit and feces, and the suspected food source can reveal the presence of the toxin. Often in cases of infant botulism, the search for the toxin in the serum is negative. It is therefore necessary the isolation of spores of *C. botulinum* from stool cultures or to identify toxins on stools. Nevertheless, anaerobic cultures can take up to 6 days to allow growth and identification of the microorganism, and identification of the toxin on stools may take from 1 to 4 days.

Dosage of the toxin in the serum can also be negative in the case of wound botulism: it is therefore necessary the isolation of the microorganism from wound swabs.

The neurophysiological tests are important to support the clinical suspicion and, from a pathophysiological point of view, they are the expression of a presynaptic blockade of acetylcholine release.

The sensory conduction studies are normal. The motor conduction studies show a reduced amplitude of the compound muscle action potential (CMAP) with normal distal latency and motor conduction velocity. The needle examination (EMG) in botulism is peculiar. Signs of denervation in the form of fibrillation and sharp waves are quite common; in fact, the toxin is a powerful blocker of the neuromuscular junction so that the muscle fibers are chemo-denervated. The motor unit potentials (MUAP) may be normal or small, of short duration and polyphasic such as myopathic MUAP.

Low-frequency repetitive stimulation (EMG-SR) determines a decremental response, while after brief exercise (10 s) or after high-frequency stimulation (30–50 Hz), an incremental response is observed. This relief is present in moderate forms or in the early stage of botulism; it must still be emphasized that even in these cases, the increase is never equal to that observed in the Lambert-Eaton syndrome and a less than 100%.

In cases of severe botulism, when acetylcholine release falls below the threshold, neither brief exercise nor high-frequency stimulation determines an incremental response. Therefore, the absence of an incremental response does not completely rule out the diagnosis of botulism. The single-fiber electromyography (SF-EMG) shows an increased jitter and blocking phenomena, indicative of a dysfunction of the neuromuscular junction [7].

7.6 Differential Diagnosis

The main differential diagnosis of botulism includes:

- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome
- Acute inflammatory polyradiculoneuritis
- Poliomyelitis
- Brainstem stroke
- Poisoning from heavy metals
- Poisoning from tetrodotoxin or shellfish

7.7 Therapy

Patients with signs and symptoms suspicious for botulism should be hospitalized immediately and subjected to monitoring of their respiratory function in order to identify early signs of respiratory failure, which is the major cause of death in affected individuals.

Monitoring of respiratory function includes evaluation of pulse oximetry, arterial blood gas analysis, spirometry and clinical evaluation of ventilation and protection of the upper airways.

Intubation should be performed in patients with an inadequate defense of the upper airway or vital capacity of less than 30% of the appraised value. In dysphagia patients, the placement of a nasogastric tube is necessary in order to avoid the risk of aspiration; in cases of paralytic ileus, it is also necessary to start with parenteral nutrition.

From the point of view of pharmacological treatment, two botulinum antitoxin therapies are available: heptavalent antitoxin from equine serum and immunoglobulins derived from human serum [8, 9].

The first is used to treat children over 1 year of age and for adults, and the other for children under 1 year of age.

In cases of suspected botulism poisoning, the Poison Control Center must be contacted for assistance, in order to receive indications on how to treat the patient with antitoxin and how to find it.

If clinical suspicion is high, and the clinical picture is rapidly deteriorating, treatment should be started as early as possible, without waiting for the results of the diagnostic tests.

The heptavalent antitoxin contains antibodies with 7 of the 8 toxins produced by *Clostridium botulinum* (A to G) and is administered intravenously. The most common side effects include headache, fever, shivers, rash, itching, and nausea. Since the antitoxin is derived from horse serum, anaphylaxis and serum sickness can occur. Some studies have reported an incidence of 20% for serum sickness and 3% for anaphylaxis [10]. Immunoglobulins derived from human serum are administered intravenously in cases of infant botulism in children younger than 1 year.

Treatment with antibiotics is not supported by clinical trials: however, antibiotics are recommended in the case of wound botulism after administering antitoxin [11]. Penicillin G is generally used (three million units IV every 4 h for adults), which

provides adequate coverage against other clostridial species. In patients who are allergic to penicillin, an alternative is metronidazole (500 mg IV every 8 h). However, antibiotics are not recommended in cases of infant botulism or gastroenteric contamination in the adult, as the lysis of intraluminal *C. botulinum* could increase the amount of absorbed toxin.

7.8 Prevention

Since most botulism cases come from food contamination, the most critical aspect of prevention is the proper handling and preparation of food. Respecting appropriate standards for cooking times, pressure, and temperature when preparing canned and preserved foods at home will help to destroy the spores. Food contained in damaged cans (cans with cracks, holes, dents, or bulges) should not be consumed. Finally, botulinum toxin is highly heat sensitive; home-canned food must therefore be boiled for at least 10 min before eating it, in order to make it safe.

Children who are less than 1 year old should not eat honey to prevent infant botulism. The most important measure for preventing wound botulism is to properly assess and treat infected wounds.

7.9 Prognosis

Patients with botulism generally require prolonged periods of hospitalization—from 1 to 3 months. Thanks to the supportive care and early treatment of respiratory failure, mortality has been reduced and accounts for 5–8% [12]. The death rate for infant botulism, the most common form in the United States, is less than 1% [13]. In minor cases we generally see a complete recovery, while in severe cases, long-term ventilation may be needed, and dysautonomic disorders and fatigue may persist for years.

7.10 Guidelines and Management Aspects in Neuromuscular Junction Diseases

In recent years, guidelines have been drafted about ocular and generalized myasthenia gravis (myasthenia gravis during pregnancy) [14–16]. There appear to be no guidelines regarding botulism. In the following table, we have summarized the most important points of these guidelines.

Myasthenia gravis in pregnancy: guidelines of a multidisciplinary working group of the United Kingdom (UK)
Norwood et al. [14]
Key points
Importance of preconception planning
Pyridostigmine, cortisone (at lower doses), and azathioprine can be used
Mycophenolate and methotrexate are teratogenic and contraindicated in pregnancy
Monitoring of gestational diabetes in patients on steroid therapy
Aim for vaginal delivery supported by an experienced multidisciplinary team
Monitoring of the newborn baby after giving birth because of the risk of transient neonatal myasthenia
Giving birth at home is not recommended
EFNS/ENS guidelines for treating ocular myasthenia
Kerty et al. [15]
Key points
Start pyridostigmine
Add steroid if the symptoms are not controlled (necessary in most cases)

Next step azathioprine
Some reports suggest that thymectomy can reduce the risk of secondary generalization
Generalized myasthenia: Guidelines from the Association of British Neurologists
Sussman et al. [16]
Key points
First-line tests: anti-AChR antibodies, thyroid function tests, radiological study of the thymus
Second-line tests: anti-MuSK antibodies, neurophysiology, brain NMR
The guidelines provide protocols of "dosage to increase" for pyridostigmine and steroids both for ocular and generalized myasthenia, including the option of alternate-day administration
Attention is given to the prevention of osteoporosis
Azathioprine as a first-line treatment in patients who do not achieve remission with prednisolone or who require long-term therapy with doses above 15–20 mg every other day
Use of IVIg and plasmapheresis in myasthenic crisis
Thymectomy should be performed in a specialized center by an experienced surgeon
Thymectomy in MG not associated with thymoma is a "reasonable" option for patients <45 years who test positive for anti-AChR Ab

7.10.1 Criteria for Patient Management

The management needs of myasthenic patients vary according to their clinical conditions:

(a) With exclusive involvement of the ocular district, the patient can start both a diagnostic and therapeutic path.
(b) Patients suffering from mild/severe generalized weakness, especially if associated with symptoms concerning

bulbar and respiratory innervated musculature, must be hospitalized in order to quickly define the diagnosis and to start the appropriate treatment protocol.

(c) Patients without severe bulbar impairment and requiring periodic immunomodulatory treatment with immunoglobulin (e.g., IV immunoglobulin) can be managed in an outpatient setting. A brief period of hospitalization may be taken into consideration in the case of chronic apheretic treatment through plasmapheresis/immunosorbent.

Emergency treatment is suitable for patients who have deficits in bulbar muscle innervation which pose a danger to the patient's safety; patients suffering from swallowing and breathing deficits are included in this category. Under these conditions, hospitalization is necessary for an adequate clinical assessment, to define the degree of ventilatory autonomy and to position nasogastric tube for feeding and therapy administration. However, treatment with steroids must be given when the patient is hospitalized because of possible further deterioration of the clinical picture due to therapy initiation.

Patient follow-up provides a periodic reassessment by means of outpatient visits; the reassessment deadlines depend on the clinical picture and the type of treatment undertaken. In particular, patients on steroid treatment are reassessed every 2–3 months for the appropriate changes in current dosage of the steroid in progress. Patients exclusively treated with immunosuppressant medication may be reassessed at less frequent intervals; periodic monitoring of blood counts is necessary, in order to highlight the specific side effects of the drug being administered.

The myasthenic patient is managed through an interdisciplinary approach which involves many professionals and several departments and services. In particular:

- The department of neurology and neuromuscular diseases outpatients service, as points of reference for the diagnosis and therapy of the myasthenic patient
- Neurophysiological services, for the neurophysiological diagnosis

- Radiology/neuroradiology facilities, to study the mediastinum by chest CT or MRI scan or to perform brain NMR when a differential diagnosis is needed for patients with complex disorders of the brain stem, or in any case with relevance to the central nervous system
- Dialysis services or transfusion centers, when plasmapheresis treatments are necessary
- The intensive care unit, for assessing patients with respiratory failure and managing patients who require mechanical ventilation
- Analysis laboratories for detecting antibodies
- Day-hospital service for immunomodulatory treatment with immunoglobulin.

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