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Case report

Botulism during SARS-CoV-2 pandemic: The importance of differential diagnoses

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ABSTRACT

Botulism is a neuroparalytic syndrome caused by a neurotoxin produced by *Clostridium botulinum*. We describe a patient with neurological symptoms associated with intoxication by *Clostridium botulinum* and infection by SARSCoV2. This report underlines that it is mandatory, even in case of SARS-CoV-2 positivity, to investigate all the causes of a clinical pattern.

1. Introduction

Botulism is a neuroparalytic syndrome caused by a neurotoxin produced by the bacterium *Clostridium botulinum* and rarely by *Clostridium butyricum* or *Clostridium barati*. *Clostridium botulinum* is a gram-positive, spore-forming, rod-shaped, anaerobic bacterium. It is generally classified into 8 serotypes (from A to H) according to the antigenicity of the toxin. Only some type of toxins (A, B, E and rarely F, G, H) can cause botulism in humans. Early manifestations include blurred vision, droopy eyelids, diplopia, dysarthria, and dysphagia. Muscle weakness occurs in descending pathway: head muscles, muscles of the upper limbs, respiratory muscles and muscles of the lower limbs. If not treated, it is potentially deathly due to respiratory insufficiency.

Considering the SARS-CoV-2 pandemic, in the evaluation of a patient with neurological symptoms, this infection must be considered in the differential diagnosis. Neurological symptoms and manifestations resulting from COVID-19 can occur before, during, and even after respiratory involvement [1,2]. Heterogeneous neurological manifestations have been reported in patients with COVID-19 infection: Central Nervous System manifestations including headache, dizziness, impaired consciousness, acute cerebrovascular disease, epilepsy, and Peripheral Nervous System manifestations such as hyposmia/anosmia, hypogeusia/ageusia, muscle pain, and Guillain-Barre syndrome [3]. Among these various manifestations, some of them such as vision loss, diplopia, nausea and vomiting, focal descending neurological deficits are symptoms attributable also to a botulism-like clinical pattern [4].

We describe a case of intoxication by *Clostridium botulinum* and infection by SARSCoV2.

2. Description of the case

A 16-years old woman with type 1 diabetes presented to our pediatric emergency department with visual disturbances (including blurred vision and photophobia), droopy eyelids, dry mouth, conjunctival hyperemia and general fatigue since 7 days.

Abbreviations: NRCB, National Reference Centre for Botulism; BoNT/B, Botulinum Neurotoxin B; H-BAT, Botulism Antitoxin Heptavalent.

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She did not have cough, sore throat, headache, loss of taste or smell or nose congestion. The physical examination did not reveal any focal deficits, respiratory distress or reduced strength in the extremities.

Focusing on her eyes, the patient showed a mydriatic pattern. Furthermore, the pupillary light reflex was unresponsive. She referred general fatigue, progressive dysphagia, difficulty with mastication, eye and face muscle movement. She reported last evacuation 10 days earlier.

The patient's mother was conducted to our adult department of emergency with similar signs and symptoms while her father was in good clinical condition.

We interviewed the patient and her father to find out more data about her medical history and the meals she had eaten in the last few days, especially homemade food.

We found that ten days earlier, they had eaten home-made tuna in oil and her father reported to have eaten a smaller amount. The following night they had gastrointestinal symptoms such as abdominal pain and vomiting.

The routine blood tests were negative. An antigenic swab test for SARS-CoV-2 was performed, resulting negative.

Considering the history, to exclude the diagnostic suspicion of foodborne botulism, the case was discussed to the National Reference Centre for Botulism (NRCB) [5] and 5 rectal swab samples with a sample of saline solution, resulting of the rectal washout, were sent to the NRCB in order to confirm the diagnosis. The same samples were collected in her mother and her father.

In accordance with the SARS-CoV-2 protocols of our hospital, we perform an RT-PCR for SARS-CoV-2 on nasopharyngeal swab, before admitting patients to non-Covid wards, and it resulted positive. Both SARSCoV2 target genes, ORF 1/a and E, were detected by RT- PCR assay. The patient's parents resulted negative on RT-PCR for SARSCoV2. At this point we had two main differential diagnosis, Botulism and SARS-CoV-2 infection with neurological involvement (Fig. 1).

After discussion with our poisons center the patient was not treat with the antitoxin because her clinical conditions were stable and slightly improving in comparison to the last week. Her mother had a similar disease evolution with clinical condition gradually improving so the antitoxin was not administered. The patient was moved to Pediatric Intensive Care Unit in order to monitor and prevent the possible onset of respiratory insufficiency related to neuroparalysis. In the following days we sent to the NRCB other rectal swab samples with stool samples as well to be analyzed.

Her condition remained stable and she didn't need oxygen or mechanical ventilation. On the fifth day, the neurological symptoms were gradually improving and the patient was moved to the department of Pediatrics and discharged after two days in good health conditions. Nine days later the bacterium *Clostridium botulinum* type B and the BoNT/B neurotoxin were detected in the biological samples previously sent to the NRCB. The same type of *Clostridium botulinum* and botulinum toxin were found on her mother's biological samples but not on her father's ones. The diagnosis of Botulism was confirmed. Ten days after the positivity for SARS-CoV-2 another nasopharyngeal swab was performed, resulting negative.

Two follow-up visits were made 7 days and 20 days after the hospital discharge, the patient still reported, although improving, dry mouth, constipation and weakness of the eye and face muscles.

Three months after the RT-PCR positive result, a SARSCoV2 serology test was performed resulting IgG positive, IgM negative.

3. Discussion

Our case report describes a botulinum intoxication in a COVID-19 positive patient with neurological symptoms. We believe that the case report presented contributes to the differential diagnosis of SARS-CoV-2 infection, despite the low frequency of botulism cases (according to the WHO, 475 cases are estimated each year in Europe, the United States and Canada). Foodborne botulism occurs after consumption of food with neurotoxin, produced by clostridial bacteria that contaminate inappropriately processed food, generally home-canned food [6–8]. Clinically botulism is characterized by progressive, symmetrical, descending paralysis in an afebrile patient with no sensory deficits. Early manifestations of botulism include blurred vision, ptosis, diplopia, dysarthria, dysphonia, and dysphagia. Muscle weakness usually occurs in descending order: muscles regarding head control, muscles of the upper limbs, respiratory muscles, and muscles of the lower limbs. If untreated, the intercostal muscles and the diaphragm are involved, then respiratory insufficiency occurs. Weakness of the limbs generally occurs in a proximal-to-distal pathway and is not necessarily symmetric, even though tendon reflexes are generally conserved. Autonomic dysfunction may occur as well, inclusive of intestinal ileus, mydriatic pupils, ophthalmoplegia, hypothermia, alterations in blood pressure, in the resting heart rate and urinary retention [9,10]. Our patient reported visual disturbances, droopy eyelids, dry mouth, progressive dysphagia, difficulty with mastication, constipation and general fatigue.

The clinical diagnosis remains the cornerstone to early detect botulism. It is fundamental to collect data regarding the patient's history to identify the possible sources of intoxication. The confirmation is made by detection of the toxin or the bacterium in serum, vomitus, stool or suspected food sources. Antitoxin remains the main therapeutic option for botulism and should be administered as soon as possible if the clinical suspicion is high and symptoms are progressing. The antitoxin binds to circulating neurotoxin and prevents their binding to the muscular junction. The most used antitoxin is the so called H-BAT, an equine serum heptavalent antitoxin which can bind toxins from A to G. The estimated rate of anaphylaxis is 1–2%. In our case we decided to not administer the antitoxin because her clinical conditions were stable and slightly improving. The stability of vital signs and the improvement of clinical conditions in the following days played a decisive role in our conservative treatment.

In the management of a patient with suspected botulism, myasthenia gravis (especially the Miller-Fisher syndrome) and Lambert-Eaton syndrome should be considered as differential diagnoses. Both these syndromes regard the neuromuscular junction and can be distinct from botulism using the electromyography [11].

The Guillaime-Barrè syndrome should also be considered, the clinical features are the main way to make a differential diagnosis, it is characterized by ascending paralysis, sensory deficits and high protein level in cerebrospinal fluid. Poliomyelitis should be investigated as well although its clinical pattern is typically asymmetric and fever is a key element of its presentation [11]. In our case we observed a symmetric descending neurological pattern which made possible to exclude all the previously mentioned diagnoses.

Considering the positivity of the SARS-CoV-2 molecular nasopharyngeal swab in the first day and the laboratory diagnosis of botulism confirmed nine days later, the SARS-CoV-2 neurological manifestations were a further option for the differential diagnosis.

Our patient was afebrile in the whole period, and she did not have cough, sore throat, headache, loss of taste or smell or nose congestion. She reported general fatigue and blurred vision, she had one episode of vomiting following the ingestion of the home-made tuna and, most of all, she had a severe conjunctival

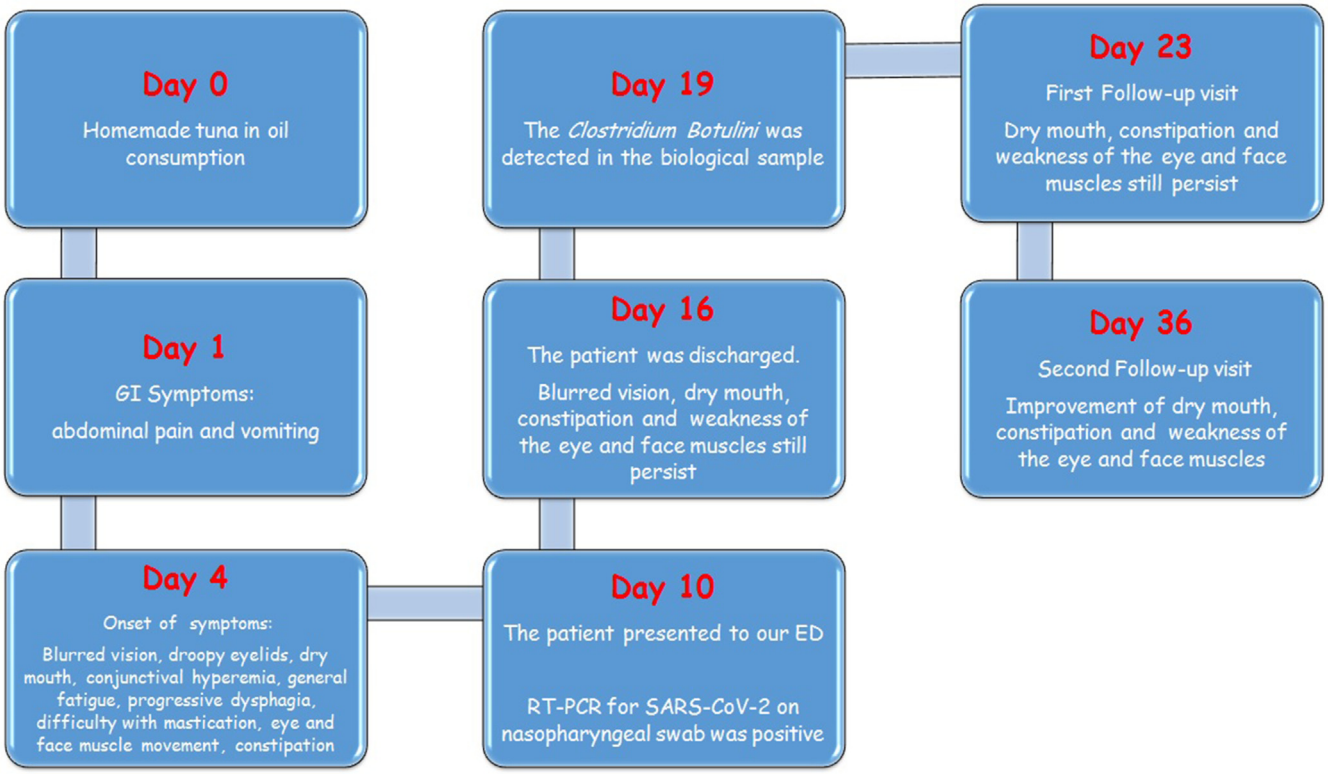

Fig. 1. Clinical course of the patient.

hyperemia. All these items made the COVID-19 differential diagnosis more likely so we had to consider the nervous system involvement of SARS-CoV-2 infection with some of its heterogeneous neurological manifestations. The blurred vision described by our patient has been previously described in a case report about bilateral reversible cortical blindness in a patient with COVID-19 pneumonia [12]. Nausea with vomiting has been reported with a prevalence of 4.6% in patients with SARS-CoV-2 infection in a recent meta-analysis [13]. Furthermore, neurological manifestations of COVID-19 may simulate neurological syndromes with a botulism-like involvement such as the Miller Fisher syndrome/Bickerstaff encephalitis [14]. General fatigue and severe conjunctival hyperemia are described in current literature as two of the major clinical markers of SARS-CoV-2 infection [15].

It must also be considered that usually patients with severe COVID-19 infection generally develop more neurological complications than non-severe patients like in our case [16,17].

4. Conclusion

Diagnosis of foodborne botulism requires a high degree of clinical suspicion. The differential diagnosis with SARS-CoV-2 infection is a challenging one. However, if there is overlap of clinical signs or symptoms, a detailed medical history should be collected in order to make differential diagnosis and early administration of botulinum antitoxin if the clinical pattern gets worse. This report underlines that it is mandatory during a pandemic period, even in positive case of SARS-CoV-2 nasopharyngeal swab, not to focus mainly on SARS-CoV-2 infection, but also to investigate all the possible causes of a certain clinical pattern to ensure the right diagnosis and treatment.

Consent

Written informed consent was obtained from the patient's parents for publication of this Case report.

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Contribution of authors

AG and LDS wrote the first draft of the manuscript; PMS, SMP were involved in the clinical investigation of the patient and conceived the manuscript; AC and GC critically reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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