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A man with laboured breathing, abdominal pain and vomiting

EDUCATIONAL CASE REPORT

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A man was hospitalised with suspected gastroenteritis and dehydration. Developments over the next few hours were surprisingly dramatic. The cause proved to be a condition that is unusual in Norway today.

A man in his 40s was hospitalised with suspected gastroenteritis and dehydration. The patient had asthma and an autism spectrum disorder. He lived in his own house and was self-sufficient, and his general condition had been normal prior to his admission.
His medical history was somewhat unclear, as his next of kin had been away for a week, and he could not be expected to give a full account of his situation. He had allegedly been vomiting for about two days, and had a cough with gagging. He also indicated pain in the throat, chest and abdomen. His next of kin stated that he found food in waste containers and that he had a lot of old food in the house.
On admission he was somnolent and weak and was mobilised into a sitting position with a great deal of help. His mucous membranes were dry, and he had diffuse abdominal tenderness. His blood pressure was 124/68 mm Hg, and fell to 92/51 while his medical details were being taken, but was stabilised by administering intravenous fluid. His urine was dark, he was afebrile and his pulse was regular at 70 beats/minute. His breathing was rapid and shallow, with a frequency of 26 per minute, employing accessory respiratory muscles. There was muffling bilaterally over the lungs.
An exploratory neurological examination revealed weakness of the extremities, equal bilaterally. It was noted that his pupils were dilated and did not react to light. There were no focal neurological deficits. His reflexes were equal bilaterally but were not graded.
Arterial blood gases showed pH 7.33 (7.36–7.44), pCO_2 6.41 kPa (4.7–5.9 kPa), pO_2 9.91 kPa (10.4–13.2 kPa), O_2 saturation 92.9 % (94–100 %) and lactate 0.9 mmol/l (0.5–1.6 mmol/l). Exploratory blood tests revealed CRP 9 mg/l (< 5 mg/l), leukocytes 12.8 giga/l (3.5–10.0 giga/l), haemoglobin 14.1 g/100 ml (13.4–17.0 g/100 ml), D-dimer < 0.4 mg/l (< 0.5 mg/l), creatinine 94 µmol/l (60–105 µmol/l), urea 13.5 mmol/l (3.2–8.1 mmol/l). Chest X-ray was perceived as normal, but the radiologist later described veiling and opacities basally on the left side of the image. Abdominal overview X-ray might suggest obstipation. Because of the report of a possible fall, headache and vomiting, a head CT was also taken, but revealed no pathology.
After examination in Acute Admissions, his condition was interpreted as asthma exacerbation with pneumonia, possibly with food poisoning as well. The patient received nebulizer treatment with ipratropium bromide and

salbutamol in addition to prednisolone by mouth and penicillin intravenously. It was assumed that his abdominal pain was due to obstipation, and he was put on macrogol.

The patient had never previously been hospitalised with asthma, or been assessed at the hospital outpatients clinic. He was a non-smoker and not taking any inhalation medicine prior to admission. His respiratory failure was therefore viewed as striking. Pneumonia was one possibility, but despite several days' illness, the patient's CRP level was low and he was afebrile. Although blood gases indicated respiratory failure type 2, a D-dimer was performed for pulmonary embolism. It was negative. Nor was the finding of obstipation on the abdominal overview X-ray to be expected with gastroenteritis with dehydration. The patient was very debilitated.

About seven hours after the man had been examined in Acute Admissions, a ward nurse contacted a doctor because the patient was sluggish and his oxygen saturation had fallen to 85 %. While the doctor was present, the patient experienced respiratory and circulatory failure.
Advanced cardiopulmonary resuscitation was started. The initial rhythm was pulseless electrical activity (PEA). After four cycles of CPR, spontaneous circulation was re-established, but 20 minutes later the patient was still not conscious. He was intubated and moved to the Intensive Care Department, where targeted temperature management was started.
His circulatory failure was primarily perceived as triggered by hypoxia. This was also most consistent with the initial rhythm of pulseless electrical activity.

The patient had strikingly fluctuating blood pressure. This was perceived as an expression of autonomic instability, and there was speculation over the cause. The question of whether it might be aortic damage or an intracerebral crisis was also raised. CT thorax, abdomen and pelvis, and a further head CT were ordered.

These scans provided no clarification. The head CT revealed no pathology. There were no signs on the CT thorax, abdomen and pelvis of pulmonary embolism or aortic dissection.
There were extensive opacities in the lower lobes of the lungs – possibly atelectasis, but infectious opacities had to be suspected. Echocardiography revealed an ejection fraction (EF) of 47 % and good contractions in all sections. No valve faults were found. A lumbar puncture was performed, and findings were normal.
Although there were no signs of aspiration when the patient was intubated, it was assumed, in light of the CT finding, that this was the case. Medication was changed to piperacillin/tazobactam.

The hypothermia treatment was discontinued after 24 hours. The patient was woken, and was at first thought to have normal strength performance. Extubation was considered, but his oxygen saturation fell again. The cause was assumed to be stress.

Sedation was discontinued the next day, and the patient was extubated. Lack of swallowing movements and weakness in both lower extremities were noted. In the course of the day he suffered increasing respiratory failure and

had to be reintubated. Because of these findings, a neurological consultation was requested.
A clinical neurological examination revealed a reduced level of consciousness. It was not possible to communicate with him, but he showed aversive responses to pain stimuli proximally of the umbilicus.
The patient lay with half-open eyes, possible bilateral ptosis and neither opened nor closed his eyes on request. An examination of the cranial nerves revealed bilaterally equal, dilated pupils without reaction to light. Conjugated eye movements were observed, with no signs of nystagmus. There was no information as to whether he had had double vision, and no signs of facial paresis.
The patient did not squeeze hands when requested to do so, but had spontaneous, bilaterally equal movements of the upper extremities. Attempts at testing gave the impression of generally limited strength in the upper extremities. There were no signs of spontaneous movement in the lower extremities. Sensibility could not be tested because of his reduced level of consciousness. There were no signs of ataxia, no triggerable reflexes in the upper or lower extremities, and no plantar inversion.
The neurological findings could be consistent with botulism or, alternatively, with Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy, AIDP) secondary to infection in the gastrointestinal tract. This condition usually starts with sensory impairment, ambulatory difficulties and areflexia. The reason Guillain-Barré syndrome was considered a possible diagnosis was paralysis of the lower extremities and extinguished tendon reflexes. Respiratory failure at the onset of the syndrome is unusual, nonetheless, and the condition seldom involves cranial nerve affection.

In our patient, cranial nerve affection in the form of dysphagia, dilated pupils with no reaction to light and possible bilateral ptosis were early symptoms that preceded loss of sensibility and pareses. These features, coupled with the symptoms nausea, abdominal pain, possible obstipation, dry mucous membranes and the development of respiratory failure, are consistent with botulism. Normal cerebrospinal fluid also provided support for our suspicion of botulism.

In Guillain-Barré syndrome, elevated total protein in the cerebrospinal fluid is expected, although this may only develop after some days of illness. With botulism there is normally truncal weakness which spreads to the upper extremities and later to the lower extremities. Our patient, however, had flaccid paralysis of the lower extremities, but could move his upper extremities. Patients with botulism do not generally develop areflexia before the affected muscle group is completely paralysed, nor was this the case for our patient. Guillain-Barré syndrome could therefore not be excluded, even though the aforementioned findings were consistent with botulism.

In Norway, foodborne botulism is diagnosed by injecting undiluted serum from the patient intraperitoneally into mice. The diagnosis is confirmed if the mice develop pareses consistent with botulism.

The neurologist contacted the Infectious Diseases Control on-duty medical officer at the Norwegian Institute of Public Health because of the suspicion of botulism. Later the same evening the patient received botulism antitoxin. It was decided also to administer immunoglobulin because of the possibility of Guillain-Barré syndrome. Antitoxin treatment consists of a single dose, immunoglobulin therapy must be administered daily while awaiting clarification.

A stool sample was obtained from the patient. PCR analysis of faeces for *Campylobacter* was positive, but the bacteria could not be cultured. A further lumbar puncture was performed after five days, but the results were still normal. Samples for botulism diagnostics were sent to the Institute for Food Safety and Infection Biology, the Norwegian University of Life Sciences, Oslo Branch. Four days later, the botulism diagnosis was confirmed – after two mice that had been injected with serum from the patient developed clear symptoms of botulism and died.

The Nordic standard method of intraperitoneal injection of mice was used (M-HL 5/NMKL 79). The test should be conducted early in the course of the disease, as the toxin binds to synapses in time, which may cause a false negative result. The stool test for PCR analysis was taken in connection with suspected gastroenteritis on admission and as part of the workup in connection with possible Guillain-Barré syndrome. The fact that our patient tested positive was not really surprising, given that he had eaten spoilt food.

The significance of subsequent findings is uncertain. The patient had no diarrhoea symptoms; on the contrary, he had obstipation as part of the botulism. The failure to culture the *Campylobacter* in the stool sample also weakened suspicion of this infection.

The connection between Guillain-Barré syndrome and *Campylobacter* infection is well known. The latter is the infection that most frequently precedes the syndrome. In a British study with 103 participants, 26 % of the patients with Guillain-Barré syndrome were found to have had a preceding *Campylobacter* infection (1).

The immunoglobulin treatment was discontinued. In view of expected long-term respirator treatment, the patient was given a tracheostomy. Piperacillin/tazobactam treatment continued because of assumed aspiration pneumonia.

The patient rapidly improved – respirator treatment was discontinued and the tracheostomy tube removed only four days later. After 11 days in Intensive Care, the patient was moved to an ordinary ward. He was mobilised with a walker and able to eat and drink independently. Two days later he was reported to the local authority as having completed treatment.

However, he remained in the department for a while, waiting for a rehabilitation place. A further neurological examination 18 days after the antitoxin was administered found him virtually restored to his habitual condition.

He is now ambulant without aids and has no focal neurological deficits. He has a slight limp after earlier sciatica.

The patient's house was found to be full of spoilt food, and it had to be thoroughly cleaned. Botulism is a Group A disease which is notifiable to the Surveillance System for Communicable Diseases (MSIS) in Norway, and the senior municipal medical officer charged with infectious diseases control was brought in.

Finding the exact source of the botulism was impossible under the circumstances, but there was considered to be little probability of secondary cases, as it was assumed that bacterial growth and toxin formation had most probably taken place during storage of food at his home. The patient's disease was assumed to be foodborne. A clinical examination revealed no wounds, and the patient's medical history revealed no suspicion of injection abuse.

Discussion

Botulism toxin is produced by the bacterium *Clostridium botulinum*, an anaerobic, gram positive, spore-forming rod. Foodborne botulism was first described by Justinus Kerner in 1820, after 230 people suffered "sausage poisoning" in Württemberg, Southern Germany (2).

The bacterium was identified in 1897, and was then named *Bacillus botulinus* after the Latin word for sausage - *botulus* (3). Generally speaking, botulism comprises three different disease pictures: foodborne botulism, infantile botulism and wound botulism. In rare cases, iatrogenic botulism also occurs in patients who have received botulinum toxin on a cosmetic or medical indication. The use of botulinum toxin is also known to have been considered in connection with bioterrorism – either by inhalation or injected into food (4).

Foodborne botulism was most common in the early 1900s, as the use of canning became more common. In Norway today botulism is most frequently seen in connection with fish fermentation and meat curing. Foodborne botulism is now a rarity in Norway, with 39 reported cases in the period 1977–2016 (5). During the same period there was one death.

Prodromal symptoms of foodborne botulism are nausea, vomiting, abdominal pain, diarrhoea, dry mouth and sore throat. Our patient had most of these symptoms at the time of admission, but they are nonspecific, and may have a number of causes.

The neurological symptoms developed by degrees: ptosis, double vision, slurred speech, symmetrical paralysis, urine retention and obstipation. Patients are not normally febrile, and the cerebrospinal fluid is expected to be normal. Sensory effects other than blurred vision are not normal. Symptoms of autonomic instability, with gastrointestinal dysfunction, changes in resting pulse, loss of response to hypotension and change of position, hypothermia and urine retention may occur. Prior to diagnosis our patient appeared to have pronouncedly fluctuating blood pressure.

Patience is important in the treatment, as it may take up to 100 days for an improvement to occur (6).

Botulism is treated with a single dose of botulism antitoxin manufactured from the blood of an immunised horse or sheep. According to the infection prevention guide from the Institute of Public Health, the institute is responsible for the supply of antitoxin in Norway. Outside the institute's opening hours, the antitoxin can be ordered from Vitus Pharmacy at Jernbanetorget, Oslo (5). When botulism is suspected, it is important to start treatment rapidly, and not wait for a final diagnosis.

Spores of *C. botulinum* are very hardy, tolerating heating up to 100^{0}C for at least four hours. Under suitable conditions, the spores germinate into toxin-producing bacteria. A temperature of 25–37^{0}C is ideal for growth, but some types can grow at temperatures from 4^{0}C. In foodborne botulism, the toxin is already in the food that is consumed, and the incubation period is therefore shorter than, for example, wound botulism. It is normally 12–36 hours, but may vary from hours to up to a week (6).

Our patient found much of his food in waste containers. Looking for food that is still edible in the waste containers of food shops has become more and more popular – a reaction to the discarding of extensive quantities of still edible food. The phenomenon is called "dumpster diving". Those who engage in the practice believe that seeing, smelling and tasting the food can determine whether it is spoilt. This is not always the case when it comes to botulinum toxin, because some types of toxin do not change the odour, taste or appearance of food. It gradually emerged that our patient not only found his food in containers, but that he also stored it for long periods, sometimes without adequate refrigeration.

The municipal infection prevention doctor must be contacted immediately on suspicion of botulism, so that infection tracing can begin. In addition to inspecting food, household waste should be examined, and this possibility may be lost if there are delays.

Botulism diagnostics takes time. This is undesirable for the individual patient, who may have to be treated for possible differential diagnoses while waiting for a final answer, with the risk of side effects. While waiting for results from the mouse bioassay, our patient was treated with immunoglobulin, as Guillain-Barré syndrome could not be excluded. Waiting for a diagnosis also means that extensive infection tracing work must be initiated before a final diagnosis can be made.

If foodborne botulism is suspected, serum from the patient must be sent to the Institute for Food Safety and Infection Biology in Oslo. In our experience, it may take time, for various reasons, from the dispatch of the sample until an answer is received. Knowledge of the toxin type facilitates the work of tracing the infection, but it is not possible to have the toxin type determined in Norway. Sample material can be sent to the State Serum Institute (SSI) in Copenhagen, as is the case for wound botulism.

Botulism is a rare condition, and inadequate knowledge of it may delay diagnosis and at worst be fatal. We have had three cases of foodborne botulism at our hospital in the course of eight months. All were confirmed by tests on mice.

No infection connection has been found between the cases, but the work of tracing the infection was difficult because of delays. All three patients had to have respirator treatment, and two suffered respiratory failure before being intubated. Respiratory failure is the main cause of death in connection with botulism.

The patient described in this article was the first of the three, and his respiratory failure was initially found inexplicable. He had already suffered respiratory and circulatory failure before the diagnosis was suspected. Owing to close follow-up from the ward nurse, a doctor was present when the failure occurred, with the result that appropriate action could quickly be taken.

Patients with inexplicable respiratory failure should be closely monitored. We suspect that botulism is an under-diagnosed condition.

The patient has consented to the publication of the article.

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