Case Report

Bacillus cereus, an unusual cause of fulminant liver failure: diagnosis may prevent liver transplantation

Mohamed Saleh,1,2† Malik Al Nakib,2,3† Sébastien Jacqmìn,1 Sébastien Ghiglione,1 Nicolas Verroust,1 Claire Poyart2,3 and Yves Ozier1,2

1Service d'Anesthésie-Réanimation Chirurgicale, Groupe Hospitalier Cochin Hôtel Dieu Broca, Assistance Publique – Hôpitaux de Paris, Paris, France
2Faculté de Médecine, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
3Service de Bactériologie, Groupe Hospitalier Cochin Hôtel Dieu Broca, Assistance Publique – Hôpitaux de Paris, Paris, France

Bacillus cereus is a well-known cause of foodborne disease usually of benign course. Here, we present the case of a 15-year-old boy who developed reversible fulminant liver failure associated with rhabdomyolysis after pasta consumption. Suspecting B. cereus as the aetiological agent may prevent unnecessary liver transplantation.

Introduction

Bacillus cereus is a soil-dwelling, spore-forming, Gram-positive bacterium surviving in a wide variety of environments. It is a known food-poisoning pathogen but is also responsible for extraintestinal infections. Some strains can produce exotoxins responsible for two different types of disease: diarrhoeal syndrome due to enterotoxins, and emetic syndrome due to cereulide toxin (Stenfors Arnesen et al., 2008). The illness is generally considered mild and short-lasting. Rare fatal cases have been reported involving healthy young persons (Dierick et al., 2005; Mahler et al., 1997). Up to now, very few cases of fulminant liver failure (FLF) have been reported. Two of these were lethal, and one was observed in a child who recovered fully, avoiding liver transplantation (Dierick et al., 2005; Mahler et al., 1997; Pósray-Barbe et al., 2008). Recently, a case of acute encephalopathy with liver failure mimicking Reye syndrome was reported, with hepatic transplantation not considered for the patient (Ichikawa et al., 2010). Here we report a new case of FLF associated with a cereulide-producing B. cereus strain.

Case report

In September 2008, a 15-year-old boy was referred to our Centre for FLF. He had no past medical history, and did not take drugs or medications. The first symptoms began 30 h before admission, with acute onset of abdominal pain and emesis without evidence of a triggering factor. The following day, blood was noticed in his vomit, and he was brought to the emergency department of the nearest hospital. Blood tests showed elevated liver enzymes (alanine aminotransferase >3000 IU l⁻¹ and aspartate aminotransferase >3000 IU l⁻¹) and incipient liver failure (prothrombin ratio 52 %, factor V ratio 35 %). An upper gastrointestinal endoscopy revealed ulceronecrotic oesophagitis and gastritis. Echocardiography and Doppler ultrasonography of the liver were unremarkable. The toxicology screen was negative. The patient was seronegative for hepatitis A, C and hantavirus. He had evidence of prior hepatitis B vaccination. He was treated with intravenous rehydration and acetylcysteine. On the same day, given the rapid deterioration in the prothrombin and factor V ratios (20 % and 18 %, respectively) suggesting fulminant hepatic failure, emergency liver transplantation was considered and he was referred to our intensive care unit. On arrival, he was found to be afibrile, with tachycardia (140 b.p.m.). Laboratory results showed elevated alanine aminotransferase (4823 IU l⁻¹), aspartate aminotransferase (3729 IU l⁻¹), serum bilirubin (42 μmol l⁻¹) and creatine kinase (12 592 IU l⁻¹) and lactic acidosis (pH 7.41, bicarbonates 20 mmol l⁻¹, lactate 5.4 mmol l⁻¹). Haemoglobin was within the normal range, with a white blood cell count of 14 500 mm⁻³. The prothrombin ratio was 21 %, with factor V 23 % and factor II 34 %. Procalcitonin was 14.9 ng l⁻¹. Plasma PCR assays for the family Herpesviridae were negative. Viral serological testing was negative for herpes simplex virus, cytomegalovirus, human immunodeficiency virus and human T-cell leukemia virus, and showed past infection for Epstein–Barr virus, varicella-zoster virus and parvovirus B19. A thoracoabdominal CT scan showed non-specific hepatomegaly. A few hours later, the neurological status deteriorated with coma and the patient was immediately scheduled for emergency liver transplantation. A profuse nonbloody

†These authors contributed equally to this work.

Abbreviation: FLF, fulminant liver failure.
diarrhoea was also noticed, and stools were analysed. Two days after admission, fever appeared and treatment with intravenous piperacillin–tazobactam (4/0.5 g every 6 h) was given for 7 days for positive blood cultures showing growth of *Klebsiella pneumoniae* and *Enterobacter cloacae*, which was attributed to intestinal translocation. A leukopenia and thrombocytopenia were investigated by bone marrow examination, which detected a maturation blockade of the granulocytic series compatible with toxic injury. Bacterial, parasitological and mycological bone marrow cultures were sterile. After 3 days, the hepatic cytolysis started to decrease, and prothrombin and factor V ratios increased, leading to reconsideration of the liver transplantation indication. Clinical improvement ensued, the neurological condition fully resolved and the liver functions normalized in a few days.

A detailed history of the patient and his relatives revealed that he had eaten pasta 4 h before the first symptoms. The pasta had been cooked 4 days before, stored in a refrigerator, and was found to have an abnormal taste and smell.

Stools were tested for *B. cereus* on days 3, 4, 5, 7 and 8 after admission. To isolate *B. cereus*, a Gram-positive selective blood agar plate containing colistin and nalidixic acid was used (Oxoid). Identification of isolates was performed on the basis of Gram staining, motility, colony appearance and haemolysis, amylase production (starch hydrolysis test), API 50 CH and API 20E strips (bioMérieux), and susceptibility to penicillin. Stool cultures yielded growth of *B. cereus* with decreasing counts from 10⁵ c.f.u. g⁻¹ on day 3 to the absence of detection on day 8. To demonstrate the toxigenic potential of *B. cereus* isolates, genes encoding emetic-toxin cereulide (*ces*) and enterotoxins (*nhe*, *hbl* and *cytK*) were analysed by multiplex PCR, as previously described (Ehling-Schulz et al., 2006). Strains isolated from each stool showed the same toxin gene pattern, *ces*⁺ *nhe*⁺ *hbl*⁻ *cytK*⁻, characteristic of cereulide-producing strains (Ehling-Schulz et al., 2005, 2006; Pósřay-Barbe et al., 2008).

Moreover, these strains were not capable of producing amylase, a feature highly suggestive of cereulide-producing strains (Ehling-Schulz et al., 2004).

**Discussion**

Cereulide is plasmid-encoded (Stenfors Arnesen et al., 2008), and *B. cereus* strains producing cereulide are most frequently reported in starchy foods. Once ingested, it resists acid conditions and proteolytic enzymes of the gastrointestinal tract. Mahler et al. (1997) were the first to demonstrate a link between cereulide-producing *B. cereus* strains and FLF. They provided experimental evidence that cereulide acts as a mitochondrial toxin via fatty-acid metabolism impairment, in keeping with liver microvesicular steatosis observed in their patient. Furthermore, the occurrence of FLF with microvesicular steatosis after cereulide injection has been described in mice. It was reversible within a few weeks with a rapid decrease of hepatic enzymes and regeneration of hepatocytes (Yokoyama et al., 1999). Interestingly, liver microsteatosis was reported in the first description of lethal *B. cereus* food poisoning in Japan (Takabe & Oya, 1976). Although the presence of cereulide in the pasta could not be tested in this case, the toxin gene pattern of strains isolated from the patient’s stools was characteristic of cereulide-producing strains (Ehling-Schulz et al., 2005, 2006; Pósřay-Barbe et al., 2008).

Moreover, our report shares many of the hallmarks of *B. cereus*-associated FLF: an extremely acute onset and rapid progression of the disease in a young person, rhabdomyolysis which is also in keeping with mitochondrial dysfunction, and severe lactic acidosis (Dierick et al., 2005; Mahler et al., 1997; Pósřay-Barbe et al., 2008). The connection between the reversible bone marrow suppression of white cell precursors observed in our case and cereulide is uncertain, as β-lactam antibiotics were used and are a possible cause of leukopenia, especially for a patient with hepatic failure (Singh et al., 1993).

Pósřay-Barbe et al. (2008) recently highlighted that, given the incidence of *B. cereus* food-poisoning outbreaks, it is surprising that so few cases of *B. cereus* toxin-mediated FLF have been reported so far. They suggested that a dose-dependent effect and/or a host genetic susceptibility might explain this rarity, but it could also be an under-recognized aetiology. However, early diagnosis may not lead to efficient specific therapeutic measures that could improve outcome as disease is mainly due to preformed toxin ingestion. On the other hand, we detected *B. cereus* in the patient’s stools, and in previously described cases *B. cereus* was found in vomit and intestinal contents (Dierick et al., 2005; Mahler et al., 1997) so antibiotic treatment could help to eradicate the bacteria and stop further toxin production. Charcoal has been suggested for detoxification (Mahler et al., 1997). The hepatoprotective effect of acetylcysteine is based on its ability to replenish glutathione stores, and it could also improve mitochondrial energy metabolism (Zwingmann & Bilodeau, 2006). However, one of the reported fatal cases occurred despite high-dose acetylcysteine administration (Dierick et al., 2005). Close monitoring of hepatic function allowed our patient to avoid liver transplantation with a rapid full recovery, as described in another patient (Pósřay-Barbe et al., 2008) and in agreement with the reversible pathological effect observed in mice (Yokoyama et al., 1999).

In conclusion, this case stresses the role of toxigenic *B. cereus* as a food pathogen and the importance of suspecting this bacterial agent as a cause of FLF of unknown pathogenesis in order to defer hepatic transplantation.

**References**


Fulminant liver failure due to *Bacillus cereus*


