

Central nervous system infection by *Bacillus cereus*: a case report and literature review

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Introduction. *Bacillus cereus* is a ubiquitous pathogen that usually produces self-limiting gastrointestinal symptoms. However, in susceptible patients, it can lead to central nervous system infections which are potentially fatal.

Development. We present the case of a 10-year-old male under chemotherapy treatment for acute lymphoblastic leukemia. During the induction period he developed a brain abscess due to *B. cereus* which was diagnosed through imaging tests and direct detection in the cerebrospinal fluid. His evolution was favorable with antibiotic treatment.

Conclusions. So far, 26 other cases of central nervous system infections due to *B. cereus* have been described in literature, and besides being infrequent, they are a diagnostic challenge. However, in preterm infants, patients with hematological malignancies or central nervous system surgery, early suspicion should be established to start an appropriate antibiotic treatment and improve prognosis.

Key words. Abscess. *Bacillus cereus*. Carbapenems. Central nervous system. Critical care. Hematologic neoplasms.

Introduction

Bacillus cereus is an aerobic or facultatively anaerobic, motile, and spore-forming gram-positive rod. It belongs to the *Bacillus* genus, along with *Bacillus anthracis*, *Bacillus thuringiensis*, *Bacillus toyonensis*, *Bacillus mycoides*, *Bacillus pseudomycoides* y *Bacillus weihenstephanensis* [1]. It is widely distributed in the environment and can be found in soil, air, fomites, and fresh and salt water. Typically, it produces mild, self-limited emetic and diarrheal syndromes after consuming food contaminated with the bacteria or its toxins. In immunocompetent people it does not usually cause serious diseases and if isolated in blood samples, it is often considered as a saprophytic contaminant [2]. However, in certain patients, such as neonates, immunosuppressed patients, and central line carriers, it can produce bacteremia and other systemic infections including pneumonia or endocarditis. Central nervous system (CNS) infections due to *B. cereus* are uncommon but potentially fatal.

Development

Case report

We report the case of a 10-year-old male diagnosed with a high-risk early T-cell precursor acute

lymphoblastic leukemia, which was treated according to LAL SEHOP-PETHEMA 2013 protocol. Two years after the diagnosis he developed an early CNS relapse and, hence he was treated according to the InteReALL HR 2010 with bortezomib protocol. During induction, after being neutropenic for four weeks (20 neutrophils/ μ L) he was receiving prophylaxis with cefepime, cotrimoxazole and fluconazole. In addition, he was being treated with acyclovir for herpes simplex virus type 1 skin infection. In that context, he developed an intense holocranial headache that did not respond to common analgesics. A cranial computed tomography scan showed a hypodense lesion in the right temporal lobe. Considering the possibility of an infectious origin, a lumbar puncture was performed and cefepime was replaced by meropenem and vancomycin.

Despite remaining afebrile, the first day after the clinic onset, he developed septic shock signs, so he was transferred to the pediatric intensive care unit for inotropic and vasoactive support. Antimicrobial spectrum was broadened with gentamycin and caspofungin.

Blood analysis showed a progressive increase of C reactive protein and procalcitonin (up to 312 mg/L and 47.58 ng/mL, respectively, on the third day of evolution) with no other biochemical alterations. Hematological analysis showed pancytopenia due to chemotherapy. Microbiological blood

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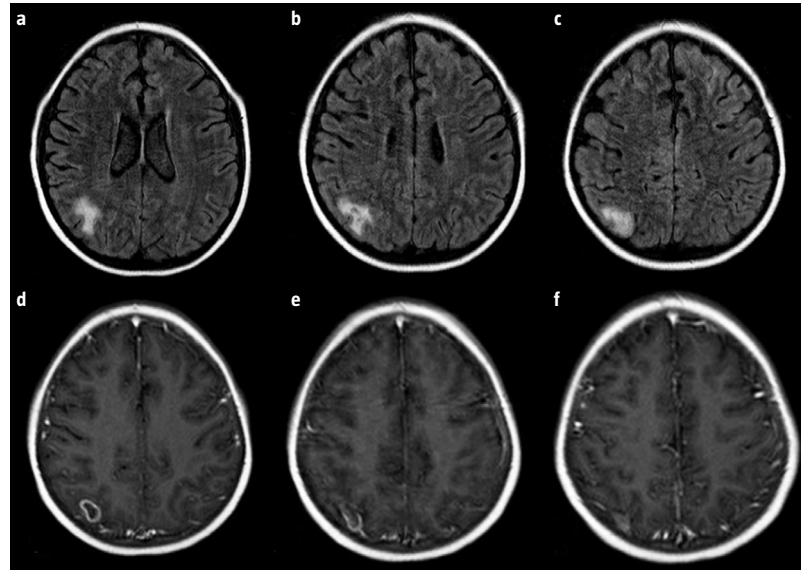
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Figure. a-c) Axial FLAIR showing a hyperintense cortical-subcortical lesion in right post-central region; d-f) Axial T₁-weighted. The lesion shows a ring-enhancing after gadolinium administration.



tests ruled out bacteremia and fungemia. All herpes viruses were negative. Urine and stool cultures were also negative. Biochemical analysis of the cerebrospinal fluid was strictly normal (glucose, 63 mg/dL; proteins, 16 mg/dL; leucocytes, 1/μL) but *B. cereus* was detected in microbiologic study (sensitive to meropenem, vancomycin, linezolid, and ciprofloxacin). Herpes simplex virus 1 and 2, herpes virus 6, cytomegalovirus, varicella-zoster virus, enterovirus, parechovirus, toxoplasma, *Neisseria meningitidis*, *Listeria monocytogenes*, *Streptococcus pneumoniae* and *Cryptococcus* were ruled out in cerebrospinal fluid.

The electroencephalogram showed a diffuse slowing of brain activity with no epileptiform activity. After removing hemodynamic support, on the fourth day, a cranial magnetic resonance was performed. It showed two hyperintense lesions in T₂ and FLAIR sequences affecting the subcortical region of the right temporal lobe and right parietal lobe. Parietal lesion presented ring-enhancing after gadolinium administration (Figure), and both lesions showed peripheral diffusion restriction. In addition, small hemorrhagic foci dispersed throughout the parenchyma were observed. The image suggested a bacterial origin by atypical germ, so these findings along with those in the cerebro-

spinal fluid, led to the diagnosis of *B. cereus* abscess.

After two weeks of treatment, the patient evolved favorably with no headache or findings on neurological examination. A control magnetic resonance showed a decrease in the size of the lesion. Vancomycin and acyclovir were suspended after three weeks and meropenem was maintained over six weeks.

Review methods

A literature review of *B. cereus* CNS infection was performed using the PubMed database. Cases in English, reported from 1990 to September 2020 under the terms '*Bacillus cereus* + Brain', '*Bacillus cereus* + Cerebral', '*Bacillus cereus* + Central nervous' were selected. 21 relevant articles were identified and data of 26 cases were available for review.

Results

Between 1990 and 2020, 26 cases of patients with CNS infection by *B. cereus* have been indexed in PubMed [3-22] (Table). When analysing the age of patients, we have considered that each age throughout life has its own characteristics, so we have separated patients into three age groups: premature infants ($n = 6$), children-adolescents between 1-18 years ($n = 5$), and adults ($n = 15$). The mean age among children was 10.2 years (95% confidence interval: 6.61-13.78) and among adults was 52.9 years (95% confidence interval: 46.16-59.58). In preterm infants, the average gestational age was 31.33 weeks (95% confidence interval: 28.2-34.5). There was no statistically significant sex difference (47.8%, women; $p = 0.11$).

Patients reviewed presented three major predisposing factors. The most frequent was neutropenia (65.4%), followed by prematurity (23.1%) and CNS surgery (11.5%). Previous history of neurosurgical intervention was only present in the group of adults (2 patients). 72% of patients had a central line (all of them were neutropenic patients) and there was only one patient without a clear predisposing factor.

Almost all neutropenic patients (94,1%) presented some underlying haematological disease. Overall, the most frequent was acute myeloid leukaemia (58.8%), followed by acute lymphoblastic leukaemia (23.5%). Myelodysplastic syndrome and aplastic anaemia with bone marrow transplant were found in one patient each. By age groups, the most frequent malignancy among adults was acute myeloid

Table. Patients with CNS infections due to *Bacillus cereus*.

	Age/Sex	Underlying situation	Sample	Clinical picture	Outcome	Treatment	Image	LP
Koizumi et al, 2020	54/F	AML (neutropenia)	Blood + CSF	Headache, altered consciousness, meningeal signs, fever	Alive	MEPM, VCM, LZD	Meningeal inflammation, abscesses	+
Brouland et al, 2018	64/M	AML (neutropenia)	Blood	Headache, coma, fever	Dead	MEPM, VCM, AMK	Lenticulostratial bleed, cortico-subcortical occipital hypodensity.	-
Saigal et al, 2016	51/M	High-grade glioma (CNS access)	Tumor biopsy	Headache, altered consciousness, seizures, fever	Alive	PIPC	Abscess	-
Melmed et al, 2016	34/F	ALL (neutropenia)	Autopsy	Altered consciousness	Dead	N	Multiple abscesses	-
Vodopivec et al, 2015	32/F	AML (neutropenia)	Biopsy	Headache, visual disturbances, fever	Alive	VCM	Abscess	-
Vodopivec et al, 2015	58/F	AML (neutropenia)	Autopsy	Altered consciousness, seizures, fever	Dead	VCM	Subarachnoid hemorrhage, intraparenchymal hemorrhage, abscess	-
Vodopivec et al, 2015	54/F	AML (neutropenia)	Autopsy	Altered consciousness, seizures, fever	Dead	DPM, VCM, LFX	Meningeal inflammation, abscess, infarcts (watershed)	+
Vodopivec et al, 2015	50/F	AML (neutropenia)	Autopsy	Headache, visual disturbances, meningeal signs, fever	Dead	VCM	Diffuse brain edema, tonsillar herniation	-
Vodopivec et al, 2015	52/M	AML (neutropenia)	Autopsy	Altered consciousness, fever	Dead	VCM	Subarachnoid hemorrhage, intraparenchymal hemorrhagic foci, diffuse brain edema	-
Dabscheck et al, 2015	5/M	ALL (neutropenia)	Blood	Fever	Alive	MEPM	Abscess	-
Hansford et al, 2014	8/M	ALL (neutropenia)	Blood	Headache, altered consciousness, fever	Alive	MEPM, CPFX, VCM	Multiple abscesses	-
Stevens et al, 2012	73/F	AML (CNS access)	CSF	Headache, altered consciousness, meningeal signs, fever	Alive	VCM, CFP	N	+
Drazin et al, 2010	32 w/F	Prematurity	Blood	Altered consciousness	Alive with sequels	VCM, GM, MEPM, drainage	Multiple abscesses	+
Ichikawa et al, 2010	11/M	No	Stool	Seizures, fever	Alive	Methylprednisolone	Hyperintense lesions (cortex and watershed)	+
Manickam et al, 2008	34 w/M	Prematurity	Autopsy	Seizures	Dead	AMP, GM, VCM	Abscesses	+
Kuwabara et al, 2006	54/F	AML (neutropenia)	Blood	Coma, fever	Alive	VCM, MEPM	Multiple abscesses	-
Lequin et al, 2005	30 w/N	Prematurity	Blood + CSF	Seizures, fever	Dead	N	Intraparenchymal hemorrhagic foci	+
Lequin et al, 2005	28 w/N	Prematurity	Blood + CSF	Fever	Dead	N	Multiple abscesses	+

Table. Patients with CNS infections due to *Bacillus cereus* (cont.).

	Age/Sex	Underlying situation	Sample	Clinical picture	Outcome	Treatment	Image	LP
Lequin et al, 2005	34 w/N	Prematurity	Blood	Seizures, fever	Dead	N	Intraparenchymal hemorrhage	+
De Almeida et al, 2003	16/F	AA with BMT (neutropenia)	Blood + CSF	Seizures, altered consciousness, meningeal signs, fever	Dead	CAZ, IPM	Normal CT	+
Psiachou-Leonard et al, 2002	11/M	Rhabdomyosarcoma (neutropenia)	Blood + Biopsy	Seizures, fever	Alive	Amphotericin B, CTX, CP	Multiple abscesses	-
Mori et al, 2002	60/M	MDS (neutropenia)	Blood	Altered consciousness, fever	Alive	GM, PPM, CLDM, CPFX	Abscess	-
Sakai et al, 2001	67/F	ALL (neutropenia)	Blood	Headache, fever	Dead	Minocycline, VCM, LFX, CP, drainage	Multiple abscesses	-
Chu et al, 2001	26 w/M	Prematurity	CSF	Bulging fontanel, irritability, fever	Dead	AMK, VCM	Diffuse brain edema, meningeal inflammation	+
Motoi et al, 1997	64/M	AML (neutropenia)	Blood	Vomiting, coma, fever	Dead	GM, PIPC, CPZ	Normal CT	-
Marley et al, 1995	26/M	AML (neutropenia)	Blood + Autopsy	Dizziness, visual disturbances, seizures, fever	Dead	CAZ	Multiple abscesses	-
Rollán-Martínez-Herrera et al (present article)	10/M	ALL (neutropenia)	CSF	Headache, hemodynamic instability	Alive	MEPM, VCM, GM	Multiple abscesses	+

AA: aplastic anemia; ALL: acute lymphoblastic leukemia; AMK: amikacin; AML: acute myeloid leukemia; AMP: ampicillin; BMT: bone marrow transplant; CAZ: ceftazidime; CFP: cefepime; CLDM: clindamycin; CNS: central nervous system; CP: chloramphenicol; CPFX: ciprofloxacin; CPZ: cefoperazone; CTX: ceftriaxone; CSF: cerebrospinal fluid; DPM: daptomycin; F: female; GM: gentamicin; IPM: imipenem; LFX: levofloxacin; LP: lumbar puncture; LZD: linezolid; M: male; MDS: myelodysplastic syndrome; MEPM: meropenem; N: not known; PIPC: piperacillin; PPM: pampipenem; VCM: vancomycin; w: weeks.

leukaemia (76.9%) while in the group of children and adolescents it was acute lymphoblastic leukaemia (50%).

Manifestations of *B. cereus* in the CNS are varied. Abscesses were the most frequent finding (68%), specifically, multiple abscesses (44%). Haemorrhagic lesions were also frequent, both intraparenchymal haemorrhages (16%) and subarachnoid haemorrhages (8%). 19.2% of patients showed inflammatory lesions or diffuse cerebral oedema, and meningeal inflammation was present in 12% of cases. The most used imaging test for both diagnosis and follow-up was magnetic resonance.

Fever was the most frequent sign (96%), followed by altered level of consciousness, including coma (57.7%); and seizures (38.5%). Signs of meningeal irritation were observed in 19.2% of the patients and vomiting in 11.5%. Among patients able to report symptoms (not premature infants), headache was a frequent symptom (40%) and visual dis-

turbances (photophobia and blurred vision) were reported in 7.6% of cases.

In most cases (57.7%) *B. cereus* was identified by blood cultures. Direct culture of a nervous tissue sample (both in biopsy and autopsy) provided the diagnosis in 48.5% of the patients. Lumbar puncture was performed in less than half of the cases (42.3%), as it was considered an unsafe test due to underlying haematological alterations and the mass effect of the brain lesions. *B. cereus* was detected in the cerebrospinal fluid in 54.5% of the patients in whom lumbar puncture was performed.

CNS infections by *B. cereus* are a serious clinical condition, with an overall mortality of 57.7% in our series. Between groups, the differences in mortality were statistically significant, with lower mortality in the group of infections due to CNS interventions (0%), followed by the group of neutropenic patients (58.82%) and premature infants (85.71%). Vancomycin was the most widely used antibiotic (53.8%

of the cases), however it did not show association with survival. Of patients who received vancomycin, 42.9% survived and of those who did not receive it, 41.7% survived ($p = 0.95$). Depending on the antibiogram, other antibiotics were used such as carbapenems (26.9%), aminoglycosides (23.1%) and cephalosporins (19.2%). None of these antibiotics showed a survival improvement except for carbapenems. We have found statistically significant differences ($p = 0.024$) between the survival of patients who were treated with carbapenems (75%) and those who did not receive them (27.8%). Meropenem was the most used carbapenem (75% of them) and demonstrated a statistically significant improvement in survival ($p = 0.02$). 83.3% of those who received meropenem survived and only 30% of those who did not. Only two patients (one adult and one premature) required surgery to drain the abscesses.

Discussion

Patients with CNS infections due to *B. cereus* can be classified into three well-defined profiles: pre-term infants, neutropenic patients, and people with a history of CNS intervention. Most often, *B. cereus* produces multiple abscesses, reflecting a hematogenous spread of the bacteria. However, it can also lead to meningitis and encephalitis. Both in the imaging tests reviewed and in the pathological studies described so far [4,14], necrosis of the brain parenchyma is evident. Since *B. cereus* frequently affects neutropenic patients, it is likely that inflammatory response does not play a major role in pathogenesis. *B. cereus* secretes various toxins such as sphingomyelinase, phosphatidyl inositol phospholipase C, haemolysin II or pore-forming cytotoxins which have been reported as the main factors in tissue necrosis [23,24].

B. cereus has three main pathways into the body. On the one hand, anatomopathological studies demonstrate the presence of *B. cereus* in the digestive system of patients with CNS involvement [22]. Given the high co-existence of haematological malignancies, some authors have suggested that mucosal breaches caused by chemotherapy drugs such as cytarabine may be the point of entry into the bloodstream [4,25]. On the other hand, *B. cereus* produces biofilms that adhere easily to the surfaces of invasive devices such as intravenous lines or ventriculoperitoneal shunts [2]. From these surfaces, bacteria can be released into the bloodstream and spread to distant organs. The presence of biofilms is

the reason why antibiotic treatment should be prolonged and invasive devices replaced. Finally, in patients with a history of CNS intervention, a direct invasion of the pathogen occurs.

Our patient suffered from acute lymphoblastic leukaemia and most of the cases reviewed had an underlying haematological malignancy. As we have argued, these diseases and related treatments meet most of requirements for *B. cereus* invasion into the CNS. Therefore, these patients constitute a high-risk group and early diagnostic suspicion of CNS infection due to *B. cereus* should be established in the presence of fever and neurological symptoms. In the case we report, the child had headache but, remarkably, he did not develop fever despite showing signs of shock. Analgesics with antipyretic function may be an explanation, but since he only received them if needed for pain, this possibility seems unlikely. We hypothesize that prolonged immunosuppression is the most plausible cause of absence of fever.

In our case, the blood cultures were negative, probably due to antibiotic treatment he was receiving prophylactically. We performed lumbar puncture because the abscess of our patient was small and had little associated oedema, so we considered it safe to carry it out after administration of a platelet pool. The definitive diagnosis was made through the identification of *B. cereus* in the cerebrospinal fluid. Since the lumbar puncture was non-traumatic, haematogenous contamination seems unlikely. Considering the profitability of the individual tests, whenever possible, both blood cultures and lumbar puncture should be performed.

B. cereus produces beta-lactamases and is resistant to penicillins and cephalosporins, therefore vancomycin is recommended as empirical treatment once this bacterium has been identified [26]. Other antibiotics such as aminoglycosides, clindamycin, or erythromycin may also be effective [14]. Interestingly, despite the small sample size, we found statistically significant differences between the survival of patients who received carbapenems and those who did not. This may be due to an adequate profile of carbapenems against *B. cereus*. They are bactericidal antibiotics active against gram-positive bacteria as well as against anaerobic species. Moreover, both imipenem and meropenem cross the blood-brain barrier and meropenem, apart from having demonstrated an improvement in survival in our series, has few adverse effects on the CNS [27,28]. Therefore, it could be a good option to empirically use in both, acute meningitis, and brain abscesses until antibiogram results are available.

Conclusions

CNS infections due to *B. cereus* are a heterogeneous group of entities with high overall mortality. Early suspicion in at-risk patients and adequate antibiotic treatment are essential to improve the prognosis.

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Infección del sistema nervioso central por *Bacillus cereus*: descripción de un caso y revisión de la bibliografía

Introducción. *Bacillus cereus* es un patógeno ubicuo que, habitualmente, produce síntomas gastrointestinales autolimitados. Sin embargo, en pacientes susceptibles, puede dar lugar a infecciones del sistema nervioso central potencialmente mortales.

Desarrollo. Presentamos el caso de un varón de 10 años en tratamiento quimioterápico por leucemia linfoblástica aguda. Durante el período de inducción desarrolló un absceso cerebral por *B. cereus* que fue diagnosticado mediante pruebas de imagen y detección directa en el líquido cefalorraquídeo. Su evolución fue favorable con tratamiento antibiótico.

Conclusiones. Hasta ahora se han descrito en la bibliografía otros 26 casos de infección del sistema nervioso central por *B. cereus*, que, además de ser infrecuentes, suponen un reto diagnóstico. Sin embargo, en los recién nacidos prematuros, en pacientes con neoplasias hematológicas o con antecedentes de cirugía del sistema nervioso central, debe establecerse una sospecha temprana para iniciar un tratamiento antibiótico adecuado que mejore el pronóstico.

Palabras clave. Absceso. *Bacillus cereus*. Carbapenémicos. Cuidados críticos. Neoplasia hematológica. Sistema nervioso central.