Cefepime-Associated SIRPIDs in a Patient With Normal Renal Function

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Abstract

Cefepime has been associated with encephalopathy and with nonconvulsive seizure activity, primarily in patients with renal impairment. Here, we report a case of cefepime-associated encephalopathy in a patient with normal renal function with stimulus-induced rhythmic activity seen on electroencephalogram, which resolved on discontinuation of cefepime. We bring this to the attention of the neurohospitalist community, as cefepime is widely used in the hospital setting, and cefepime-related neurotoxicity may go overlooked, especially in patients with normal renal function. Neurologists must recognize drug-related patterns, as the treatment is removing a medication rather than adding an antiepileptic medication.

Keywords

neurotoxicity, electroencephalography, electrophysiology, neurohospitalist, infectious disease medicine

Introduction

Cefepime is a fourth-generation cephalosporin frequently used for nosocomial infections, now known to cause severe but reversible encephalopathy or nonconvulsive seizure activity in the setting of renal impairment. We present a case of a patient with normal renal function in whom cefepime produced encephalopathy with stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs).

Case Description

A 67-year-old woman from Haiti presented with fever and back pain and was found to have osteomyelitis at L3 with associated epidural abscess at L3 to L4. Despite several weeks of treatment with vancomycin and piperacillin/tazobactam and later with meropenem, she had persistent fever. Additional workup revealed abscesses of the thoracic cord and iliopsoas muscle, with multifocal pulmonary nodules, and she was then transferred to a tertiary care center. Cerebrospinal fluid (CSF) analysis revealed elevated white blood cell count (15 cells/mm³, with red blood cell count 4000 cells/mm³), and CSF cultures including mycobacterial culture had no growth. Antibiotic therapy was changed to vancomycin (1000 mg every 12 hours) and cefepime (2 g every 8 hours).

Following that, she developed altered mental status with confusion and delayed responses on hospital day 4, without a focal deficit on neurological examination. On hospital day 7, she was found to have numerous, small, multifocal brain

lesions suggestive of disseminated tuberculosis, and isoniazid, rifampin, and metronidazole were added to her antibiotic regimen. Due to eyelid twitching and concern for seizure, levetiracetam and fosphenytoin were started on hospital day 8. A 24-hour electroencephalogram (EEG) performed on hospital days 8 to 9 showed bilateral slowing, with background reactivity and without epileptiform activity. Her mental status declined further on day 10, and she was intubated for a bronchoscopy procedure. Following the procedure, her mental status continued to worsen and she became comatose. Laboratory investigation of causes for altered mental status did not reveal an explanation, and her serum sodium ranged from 139 to 145 mEq/L, her liver function tests were within normal limits (aspartate aminotransferase 28 U/L and alanine aminotransferase 15 U/L), her international normalized ratio was 1.1 to 1.2, and her arterial Pco₂ was 34 to 40 mm Hg. She had no signs of raised intracranial pressure (ie, no papilledema and no Cushing response).

On hospital day 11, repeat EEG showed cyclical buildups of rhythmic slow activity which was initially read as seizure

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Figure 1. Consecutive panels from continuous video electroencephalogram (EEG) tracing showing patient background with slow activity (empty arrow) and reactivity when care provider suctions patient (black arrow). Stimulus-induced rhythmic activity is then seen in the anterior leads (arrowheads), which continued while the patient was stimulated, and which was initially interpreted as seizure activity. Longitudinal bipolar montage.

activity, and a 24-hour monitoring was initiated. A trial of valproic acid failed to improve her clinical state or the EEG pattern. The epileptiform activity was found to be stimulus related and was then categorized as SIRPIDs due to the appearance of rhythmic delta range activity after the patient was stimulated (SIRPIDs; Figure 1). Valproic acid was discontinued, and cefepime was replaced by meropenem due to concern for cephalosporin-related encephalopathy. No other medication changes were made. One day after cessation of cefepime, the patient's mental status improved and the SIRPIDs resolved. Her medication list was screened for drug interactions with cefepime, and no interactions were found.

On hospital day 18, meropenem was changed back to cefepime, which was again followed by alteration of mental status. Her mental status again improved after cessation of cefepime on hospital day 21 (EEG was not repeated during this time period).

The patient was eventually confirmed to have disseminated tuberculosis by brain biopsy with genetic sequencing. She was discharged to a rehabilitation facility on hospital day 32. This patient's renal and hepatic function remained normal throughout her course (her creatinine fluctuated between 0.4 and 0.6 mg/dL).

Discussion

Cefepime-associated encephalopathy is an increasingly recognized cause of altered mental status in the hospital setting. It typically occurs in the setting of renal failure without concomitant gross brain pathology¹⁻⁸ and can begin 1 to 15 days after cefepime initiation.⁸ Reported associated EEG patterns include rhythmic triphasic waves which are nonreactive to stimulation,¹⁻³ nonconvulsive status epilepticus with generalized spike and slow-wave or sharp and slow-wave activity,^{1,6,8,9} and generalized periodic discharges.¹⁰ One case of stimulus-responsive EEG changes has been reported previously¹¹ in a patient with renal failure and no intracranial pathology. Each of these features in isolation could warrant treatment with antiepileptic medications; therefore, investigating the potential causes of electroclinical abnormalities rather than solely treating with additional drugs is of vital importance.

Stimulus-induced rhythmic, periodic, or ictal discharges are defined as periodic, rhythmic, or ictal-appearing discharges that are consistently induced by alerting stimuli (ie, sternal rub, patient care, examination, or auditory stimuli).¹² These can occur in patients with or without unequivocal electrographic seizures. The significance of SIRPIDs and the degree to which SIRPIDs should be treated aggressively are

unclear.^{13,14} Distinguishing SIRPIDs from spontaneous ictal or rhythmic activity may influence treatment decisions; therefore, ensuring daily stimulation during prolonged EEG recording and identifying EEG changes with stimulation are crucial.

Rarely, cefepime-induced encephalopathy and epileptiform activity have been seen in patients with normal renal function, such as our patient.^{9,10} A retrospective study of 59 patients treated with cefepime who also had EEG found generalized periodic discharges in 9 patients without renal dysfunction (vs generalized periodic discharges found in 3 of 80 patients treated with meropenem), and 2 of the 9 patients had intracranial pathology (1 with subdural hematoma and 1 with ischemic frontal injury).¹⁰ Our patient had normal renal function but did have multifocal intraparenchymal lesions, and this may suggest that cefepime should be used with greater caution in patients who have brain pathology.

The appearance of encephalopathy within 4 days of starting cefepime followed by the appearance of SIRPIDs on EEG a few days later, in addition to the temporal resolution of the clinical and EEG features after stopping the medication (without any other interventions), strongly suggests cefepime as the culprit agent. This time course is consistent with previously reported cefepime-related neurotoxicity, as the reported time lag between starting the medication and the onset of symptoms ranges between 1 and 15 days.⁸ The reappearance of encephalopathy with reintroduction of the medication serves as additional confirmatory evidence.

To our knowledge, this is the first case of cefepime-associated SIRPIDs in a patient with normal kidney function. Neurologists should be aware of cefepime-associated encephalopathy, especially in patients with intraparenchymal pathology. Electroencephalogram changes related to cefepime are not limited to classic triphasic waves or generalized spike and wave activity. Electroencephalogram should be obtained if patients treated with cefepime develop altered mental status, even in the absence of renal failure, and a trial of cefepime discontinuation (if an alternative agent can be found) may be warranted prior to treatment with antiepileptic drugs.

Authors' Note

The Johns Hopkins Institutional Review Board waived informed consent for this case report, as data was collected through an approved study with a waiver of informed consent.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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