Cefepime-Induced Encephalopathy and Nonconvulsive Status Epilepticus: Dispelling an Artificial Dichotomy

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Abstract

Cefepime is a fourth-generation cephalosporin antibiotic known to have neurotoxic side effects. Recent reports have described patients on cefepime presenting with altered mentation and concurrent triphasic wave discharges on electroencephalogram (EEG). Some have described this clinical presentation as cefepime-induced encephalopathy, while others have termed it as cefepime-induced nonconvulsive status epilepticus (NCSE). We report on 4 patients who developed cefepime-associated altered mentation with triphasic discharges on EEG. A benzodiazepine trial was attempted in 3 of the patients, all of whom had improvement in the frequency of the triphasic discharges, but only 2 of whom demonstrated a concurrent partial and transient improvement in mental status. All 4 patients had normalization of mental status upon discontinuation of cefepime. We provide a literature review of prior cases and propose that these reports, including those labeled as NCSE, are best described as a cefepime-induced encephalopathy with triphasic discharges as opposed to an ictal phenomenon. We contend that aggressive treatment with anti-seizure medications is not warranted and that cefepime discontinuation is the definitive treatment. This case series and review of the literature clarifies a long-standing terminological ambiguity in a unique clinical picture that can be encountered by the neurohospitalist or other providers.

Keywords

encephalopathy, EEG, nonconvulsive status epilepticus, cefepime

Introduction

Cefepime is a broad-spectrum fourth-generation cephalosporin antibiotic that has been used in clinical practice since the 1990s.¹ There has been a growing recognition that cefepime is associated with neurotoxic effects, typically varying degrees of altered mental status often with additional symptoms of myoclonus, aphasia, clinical seizures, and agitation.² Those with renal impairment are particularly at risk for these side effects,³ although the same toxicities have been documented in patients without concurrent renal insufficiency.^{4,5} A commonly reported constellation of symptoms is altered mentation with concurrent triphasic wave (TW) discharges on electroencephalogram (EEG). These reports have variably described the same electroclinical constellation of symptoms as either cefepime-induced encephalopathy or at other times cefepime-induced nonconvulsive status epilepticus (NCSE). To this point, a clear differentiation between these 2 conditions has been lacking and it remains unclear whether these are clinically distinct phenomena or a spectrum of the same condition.

Case Presentations

Case 1

A 78-year-old female was admitted with a small right hemispheric subdural hemorrhage after a fall. Her hospital course was unremarkable with normal mentation until cefepime was initiated for pneumonia at a dose of 1 g every 8 hours. Two days after cefepime initiation, the patient's mental status acutely worsened. A head computed tomography done at that time remained stable from prior, and her renal function was within normal limits. An EEG demonstrated generalized

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Figure 1. Electroencephalogram (EEG) recordings of 4 patients reported in this case series at time of EEG placement (A, C, E, G) and after receiving lorazepam (B, D, F) or after cefepime discontinuation for the patient who did not receive lorazepam (H).

periodic discharges with TW morphology (Figure 1A). On examination, she was unable to follow commands, and intermittent myoclonic jerking was noted. Her creatinine and liver function testing were normal. Due to concern that the EEG findings along with her altered mentation represented NCSE, she was administered 2 mg of intravenous (IV) lorazepam with partial improvement in mental status and concurrent transient resolution of the triphasic discharges (Figure 1B). The patient was started on maintenance levetiracetam therapy, and

cefepime was discontinued. Although there was partial transient improvement after the lorazepam dose, her mental status definitively normalized about 4 days after cefepime discontinuation.

Case 2

A 50-year-old female with a history of lung transplant for interstitial lung disease (caused by graft-versus-host disease

from a stem cell transplant done for chronic myeloid leukemia) and chronic renal impairment (baseline creatinine 2 mg/dL) was admitted with pneumonia and started on cefepime at a dose of 2 g every 12 hours. Three days after cefepime initiation, the patient became nonverbal, unable to follow commands, and demonstrated intermittent multifocal myoclonic jerking. Electroencephalogram showed generalized periodic discharges with TW morphology (Figure 1C), and her liver function testing during this time was within normal limits. Due to concern for NCSE, the patient was given 2 mg of IV lorazepam with subsequent decrease in frequency of the triphasic discharges on EEG (Figure 1D), but no improvement in her mental status. Levetiracetam was also added and cefepime was concurrently discontinued. The patient's mental status normalized about 5 days after antibiotic discontinuation.

Case 3

A 57-year-old female with type 2 diabetes, ischemic cardiomyopathy, and chronic kidney disease (baseline creatinine 1.7 mg/dL) was admitted for heart failure and soon after empirically initiated on cefepime for fever at a dose of 1 g every 8 hours. Her mental status deteriorated within a day of therapy initiation with loss of orientation, diminished speaking (although still verbal), and difficulty following commands. Electroencephalogram revealed generalized discharges with TW morphology (Figure 1E) with concurrently normal liver function testing. Due to concern for NCSE, the patient received 1 mg lorazepam with partial clinical improvement (became more verbal and slight improvement in ability to follow commands), while EEG concurrently showed resolution of triphasic discharges (Figure 1F). Although her cognition partially improved, she then developed visual hallucinations. Cefepime was discontinued and her mental status returned to baseline 1 day after antibiotic discontinuation.

Case 4

A 70-year-old female with a remote history of lung transplant for α -1 antitrypsin deficiency was admitted with pneumonia and started on IV cefepime at a dose of 1 g every 12 hours. Six days after antibiotic initiation, she developed altered mental status: initially disorientation that then evolved into being nonverbal and inability to follow commands. Her creatinine was at its baseline elevated state of 1.7 mg/dL, while her liver function testing was within normal limits. An EEG demonstrated generalized discharges with TW morphology (Figure 1G), which was felt to be secondary to cefepime toxicity. Cefepime was thus stopped and the patient's mental status normalized 2 days postcefepime discontinuation with associated resolution of TW discharges on EEG (Figure 1H).

Discussion

Cefepime-induced altered mental status with concurrent TW discharges on EEG has been well-documented, yet prior reports have conflictingly labeled the same phenomenon as either encephalopathy or NCSE (Table 1). Based on this dichotomized labeling, those deemed to have "NCSE" were more likely to receive one or more anti-seizure medication (ASM), while others labeled "encephalopathic" often just had their cefepime discontinued without additional interventions.^{4,7-9,11,12} Indeed, on review of prior cases outlined in Table 1, 100% of those labeled NCSE received an ASM compared to only 15% of those who were labeled as having an encephalopathy. No report prior to our case series clearly demonstrated a positive electroclinical response to ASMs (as in our case, the clinical improvements were only partial), while all earlier publications on this topic, regardless of whether they labeled the case as encephalopathy or NCSE, report resolution of the altered mentation after cefepime discontinuation.

The cefepime-induced encephalopathy versus NCSE debate has important clinical implications. We are concerned that the current dichotomized terminology is causing those labeled as NCSE to receive more aggressive therapy with ASMs and that such aggressive treatment may increase the risk of avoidable side effects. Additionally, a label of NCSE may potentially distract providers from implementing the definitive treatment (cefepime discontinuation). In situations where this clinical scenario is encountered, it is the neurohospitalist's role to provide a moderating context to the EEG interpretation, which may, indeed, be interpreted as NCSE and lead to overly aggressive treatment with ASMs.

Triphasic waves are classically considered a nonictal EEG pattern seen in toxic metabolic encephalopathies.¹³ Triphasic wave can resolve in response to benzodiazepine administration, which may lead to the misdiagnosis of this encephalopathic phenomenon as ictal.^{13,14} To avoid such mislabeling and to account for rare situations in which TWs may represent ictal activity, it has been proposed that the diagnosis of NCSE in the presence of TWs should be an electroclinical one, with a clear normalization of mental status and resolution of TW discharges on EEG in response to ASM necessary to label the condition as NCSE.^{13,15}

As evident from Table 1, no prior reports have demonstrated a clear electrographic and clinical response to anti-epileptic agents that would be necessary to meet criteria for NCSE. Our case series is the first to demonstrate both a clinical and electrographic response to benzodiazepines, albeit only a partial and transient clinical response in 2 of the 3 patients who receive lorazepam, thus not meeting criteria for NCSE.

We therefore propose that the phenomenon of cefepime-induced altered mentation with triphasic discharges is, in the majority of cases, a nonepileptic encephalopathic state that is most accurately described as an encephalopathy and best

Table 1. Reports of Cefepime-Associated Altered Mental Status With Triphasic Discharges on EEG.^a

Pt.	Age (Year)/ Gender	Days on Cefepime Prior to AMS	ASM Used	Clinical Improvement From ASM	EEG Improvement From ASM	Days to Improvement After Cefepime Discontinuation	Term Used by Authors
1 ⁶	77/M	4				3	EP
2 ⁶	71/M	3				2	EP
3 ⁶	59/F	2				4	EP
4 ⁷	71/F	5	LZP, LEV, VPA, CLN, PHE	No	Yes	3	NCSE
5 ⁸	76/M	2				3	EP
6 ⁸	66/M	3				3	EP
7 ⁸	69/F	5				5	EP
8 ⁸	81/F	4	Yes, drug name ND	ND	ND	4	EP
9 ⁸	84/M	5				4	EP
10 ⁷	52/M	2	DZP	ND	ND	7	NCSE
11 ⁷	39/F	6	DZP	ND	ND	5	NCSE
12 ⁹	58/F	8	DZP	ND	ND	5	NCSE
13 ⁹	68/F	4	DZP	ND	ND	5	NCSE
14 ⁹	74/F	4	DZP, LEV	ND	ND	5	NCSE
15 ⁴	74/F	7	PHE	ND	ND	3	NCSE
16 ¹⁰	64/M	3				ND	EP
17 ¹¹	57/F	10	LEV, PHE	ND	ND	4	NCSE
18 ⁵	64/F	5				3	EP
19 ¹²	68/M	7	CBZ			4	EP
20 ¹²	85/F	4	PHE			6	EP
21 ¹²	72/F	9				4	EP
22 ^b	78/F	2	LZP, LEV	Yes	Yes	4	
23 ^b	50/F	3	LZP, LEV	No	Yes	5	
24 ^b	57/F	1	LZP	Yes	Yes	1	
25 ^b	70/F	6				2	

Abbreviations: AMS, altered mental status; ASM, anti-seizure medication; CBZ, carbamazepine; CLN, clonazepam; DZP, diazepam; EEG, electroencephalogram; EP, encephalopathy; LEV, levetiracetam; LZP, lorazepam; NCSE, nonconvulsive status epilepticus; ND, not documented; PHE, phenytoin; VPA, valproate.

^aPatients were identified via a PubMed search for the terms “cefepime,” “encephalopathy,” “NCSE,” and “non-convulsive status epilepticus.”

^bPatients reported in current case series.

treated with the removal of the offending agent. Practitioners encountering this phenomenon must be cognizant that overly aggressive treatment with ASMs is not warranted and may lead to additional side effects without the benefits of a positive clinical response. Our experiences demonstrate that a lorazepam trial can produce partial and transient electrographic and clinical improvements and can thus be considered as an adjunct to cefepime discontinuation, but more aggressive treatment should be avoided.

This study was approved by the Duke University internal review board, which granted a waiver of informed consent because the data were collected via a retrospective chart review. The patients in this case series were identified prospectively by the authors, who were on EEG service at the times when the patients underwent EEG monitoring.

Declaration of Conflicting Interests

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