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CEFEPIME-INDUCED NEUROTOXICITY WITH PRESERVED RENAL FUNCTION: AN UNUSUAL DIAGNOSTIC CHALLENGE

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ABSTRACT

Background: Cefepime-induced neurotoxicity is reported in up to 15% of critically ill patients receiving the drug and approx. 80% of affected individuals demonstrating underlying renal dysfunction. However, approximately 20% of cases occur in patient with preserved renal function, as described by Payne *et al.* (2017)[1] We report a case highlighting the possibility of Cefepime-induced encephalopathy as a cause of neurological deterioration in critically ill patient especially with preserved renal functions. **Case description:** A 76-year-old male patient with Chronic obstructive pulmonary disease, chronic hyponatremia (sodium 118 mEq/L), hypoalbuminemia (albumin 2.5 g/dL), reduced left ventricular ejection fraction (LVEF-40%), and recurrent multidrug-resistant infections developed progressive encephalopathy within 48 hours of initiating intravenous Cefepime–enmetazobactam combination (2.5gm IV every 8 hourly) having 2 gm of Cefepime and 500 mg of enmetazobactam in each vial. Patients Glasgow Coma Scale declined from 14/15 (E4V4M6) to 9/15(E2V3M4) over period of 48 hours. Detailed evaluation of the etiology of neurological deterioration almost ruled out all structural and metabolic causes. Electroencephalography (EEG) demonstrated left fronto-temporal and right frontal epileptiform activity with diffuse cerebral dysfunction, consistent with type 1 antibiotic-associated encephalopathy pattern described by Bhattacharyya *et al.* (2026). Cefepime-induced neurotoxicity was kept as a strong possibility even with preserved renal functions. Serum creatinine remained within normal limits (0.4–0.6 mg/dL) all throughout. **Discussion:** Application of the Bradford Hill criteria supports a probable causal relationship of CIN. The EEG findings can be very specific and helps in making early diagnosis. Many non-renal risk factors such as advanced age, hypoalbuminemia, sepsis-related blood–brain barrier disruption, and chronic electrolyte disturbance should also be kept in mind while starting Cefepime in patients with such risk factors. **Conclusion:** Cefepime-induced neurotoxicity should be considered in any critically ill patient with unexplained neurological deterioration during Cefepime therapy, irrespective of renal function. **Statement of clinical significance:** This case demonstrates that CIN can occur despite preserved renal function when non-renal risk factors—advanced age, hypoalbuminemia, sepsis-related blood–brain barrier disruption, and chronic electrolyte disturbance—converge. Clinicians should maintain a high index of suspicion and obtain early EEG in at-risk patients receiving Cefepime, regardless of renal function status.

KEYWORDS: Cefepime, Neurotoxicity, Encephalopathy, Non-renal risk factors, Electroencephalography, GABA receptor antagonism, older patient.

INTRODUCTION

Cefepime is a fourth-generation cephalosporin widely used in intensive care settings for its broad-spectrum activity against Gram-positive and Gram-negative organisms, including *Pseudomonas aeruginosa*. Although generally well tolerated, Cefepime-induced neurotoxicity has emerged as a cause of clinically significant adverse drug reaction. A systematic review by Payne *et al.* (2017) identified neurotoxicity in up to 15% of critically ill patients receiving Cefepime, with 80% of affected individuals demonstrating underlying renal dysfunction.[1] The proposed mechanism involves concentration-dependent antagonism of gamma-aminobutyric acid type A ($GABA_A$) receptors, leading to neuronal hyper excitability.[2,5]

Critically, up to 20% of reported case of CIN have occurred in patients with normal renal function.[3] Non-renal risk factors—including advanced age, hypoalbuminemia, sepsis-induced blood–brain barrier disruption, and pre-existing the risk of pathology—can independently increase central nervous system Cefepime penetration from approximately 10% to as high as 45%.[2] Payne *et al.* (2017) in a systematic review reported a mean age of 66 years among affected patients,[1] and Appa *et al.* (2017) identified age greater than 65 years as a significant risk factor in 135 cases.[4] Recognition is frequently delayed in the intensive care unit because competing causes of encephalopathy dominate the differential diagnosis.

We report a case of Cefepime-induced encephalopathy in a critically ill patient with preserved renal function, to highlight the cumulative contribution of non-renal risk factors and the importance of early EEG for evaluation.

CASE DESCRIPTION

A 76-year-old male patient presented to our Emergency Department with a 2–3day history of worsening dyspnea, productive cough, decreased oral intake, and generalized weakness. He was bedridden and ambulatory only with assistance. An indwelling urinary catheter had been replaced approximately two weeks prior to presentation.

His medical history was significant for chronic obstructive pulmonary disease with home bi-level positive airway pressure (BIPAP) support, ischaemic heart disease with prior percutaneous coronary intervention (LVEF-40%) and chronic persistent AF requiring cordarone. Past history is also significant for chronic hyponatremia and a recent urinary tract infection caused by carbapenem-resistant *Escherichia coli*. There was no prior history of seizures, cognitive impairment, or known structural central nervous system disease.

On admission, vital signs revealed a heart rate of 85 beats per minute, blood pressure 120/90 mmHg, temperature 38.1°C, and oxygen saturation 88% on room air. Auscultation revealed bilateral diffuse wheezing. The Glasgow Coma Scale score was 14/15 (E4V4M6). Routine investigations revealed leukocytosis (total leucocyte count 14 860/mm^3), hyponatremia (sodium 118 mEq/L), hyperkalemia (potassium 5.4 mEq/L), hypoalbuminemia (albumin 2.5 g/dL), and preserved renal function (creatinine 0.6 mg/dL). Procalcitonin was 3.2 ng/mL. Two-dimensional echocardiography revealed a left ventricular ejection fraction of 45%.

Serum osmolality was 242 mOsm/kgH_2O with urine osmolality 325 mOsm/kgH_2O and urine sodium 48 mEq/L, supporting syndrome of inappropriate antidiuretic hormone secretion. Renal function remained preserved (creatinine 0.6, 0.4, 0.5 mg/dL on Days 1–6). Serial laboratory investigations are summarized in Table 1.

Table 1: Serial laboratory investigations during hospitalization.

Investigation	Day 1	Day 3	Day 6
Hemoglobin (g/dL)	10.2	9.6	9.2
Total leucocyte count (/mm³)	14 860	17 280	18 850
Platelet count (×10⁹/L)	299	325	326
Procalcitonin (ng/mL)	3.2		1.5
Blood urea nitrogen (mg/dL)	26	33	43
Serum creatinine (mg/dL)	0.6	0.4	0.5
Sodium (mEq/L)	118	120	123
Potassium (mEq/L)	4.5	4.5	4.1
Calcium (mg/dL)	8.4	–	–
Magnesium (mg/dL)	1.8	2.1	–
Serum albumin (g/dL)	2.5	–	–
Total bilirubin (mg/dL)	0.7	–	–
AST/ALT (U/L)	25/40	–	–
International normalized ratio	1.28	–	–
TSH (mIU/L)	1.902	–	–
Troponin I (ng/mL)	<0.01	–	–
CPK (U/L)	210	–	–

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TSH, thyroid stimulating hormone; CPK, creatine phosphokinase. 'Day 1 'corresponds to the date of admission.

Chest radiograph on admission (Figure 1) demonstrated bilateral diffuse reticulonodular opacities with hyper inflated lung fields and flattened hemidiaphragms, consistent with underlying chronic obstructive pulmonary disease. There was bilateral perihilar haziness suggesting superimposed pulmonary edema or infective consolidation.

Computed tomography of the chest (Figure 2) demonstrated bilateral ground-glass opacities and patchy consolidation consistent with multifocal pneumonia superimposed on emphysematous changes. Non-contrast computed tomography of the brain (Figure 3) revealed an incidental calcified meningioma without acute intracranial pathology.

Portable EEG performed on Day 2 (Figure 4) demonstrated symmetrical generalized theta background with frequent left fronto-temporal and right frontal sharp and slow wave discharges. These findings are consistent with type 1 antibiotic-associated encephalopathy as classified by Bhattacharyya *et al.* (2016).[7]

Clinical course and treatment

On Day 1, empirical antimicrobial therapy was initiated with intravenous Cefepime–enmetazobactam (2.5 gm IV every 8 hourly), doxycycline, oseltamivir, and corticosteroids, alongside standard supportive care. Tolvaptan 15 mg OD was initiated for persistent hyponatremia consistent with SIADH. On Day 2, the Glasgow Coma Scale declined from 14/15 (E4V4M6) to 9/15 (E2V3M4) on day 1. Both the pupils were normal in size and showing normal reaction. Thorough evaluation for sudden decline in neurological status was done. CECT brain along with TSH and NH3 levels were with in normal limits. EEG raised suspicion for Cefepime-induced neurotoxicity. Cefepime–enmetazobactam was immediately discontinued. Antimicrobial therapy was changed to intravenous meropenem and antiepileptic coverage was initiated with intravenous levetiracetam (500 mg twice daily which titrated to 1000 mg twice daily).

Differential diagnosis

Hyponatremia encephalopathy was considered but neurological deterioration continued despite gradual sodium correction; the chronicity argued against this as the primary driver.

Sepsis-associated encephalopathy was disproportionate to the degree of sepsis and the EEG pattern of focal epileptiform discharges is not characteristic of pure sepsis-associated encephalopathy.[7]

Hypercapnic encephalopathy was excluded as CO_2 levels were not very high (pCO_2- 42) and pH (7.46-7.31) was maintained all through out. Cefepime-induced encephalopathy was favoured based on convergence of Bradford Hill criteria: temporality, biological plausibility, consistency, coherence, and analogy.

Outcome

Patient didn't survive and died on 6th day of admission.

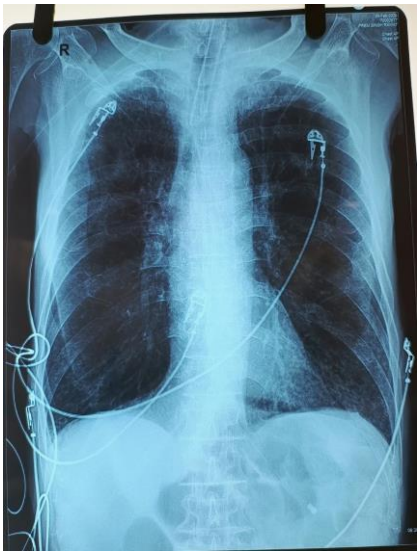

Figure 1: Chest radiograph (anteroposterior view) on admission demonstrating bilateral diffuse reticulonodular opacities with hyper inflated lung fields, flattened hemidiaphragms, and bilateral perihilar haziness.

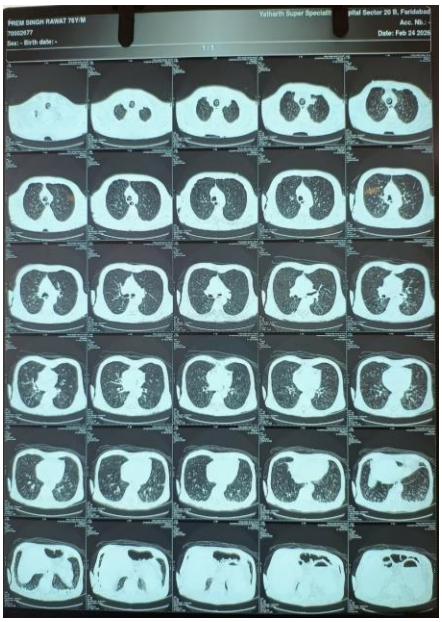

Figure 2: Computed tomography of the chest (lung window) demonstrating bilateral ground-glass opacities and patchy consolidation with underlying emphysematous changes consistent with chronic obstructive pulmonary disease and superimposed multifocal pneumonia.

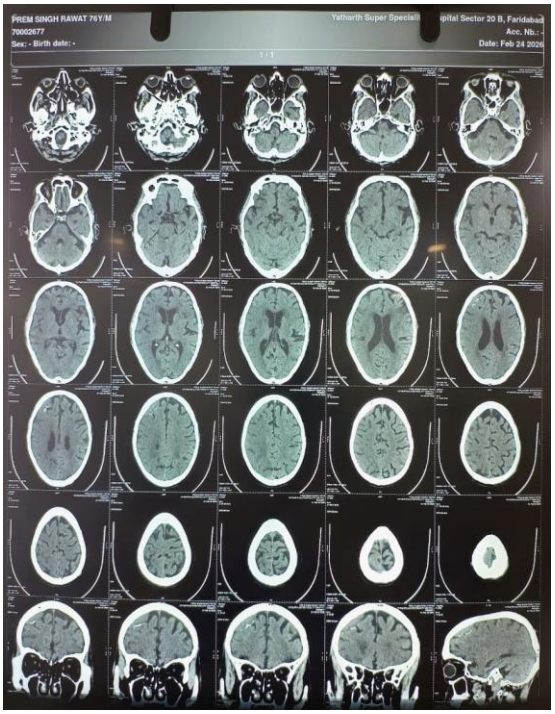

Figure 3: Non-contrast computed tomography of the brain demonstrating an incidental calcified meningioma without evidence of acute intracranial pathology, cerebral edema, midline shift, or hydrocephalus. Age-related cerebral atrophy is noted.

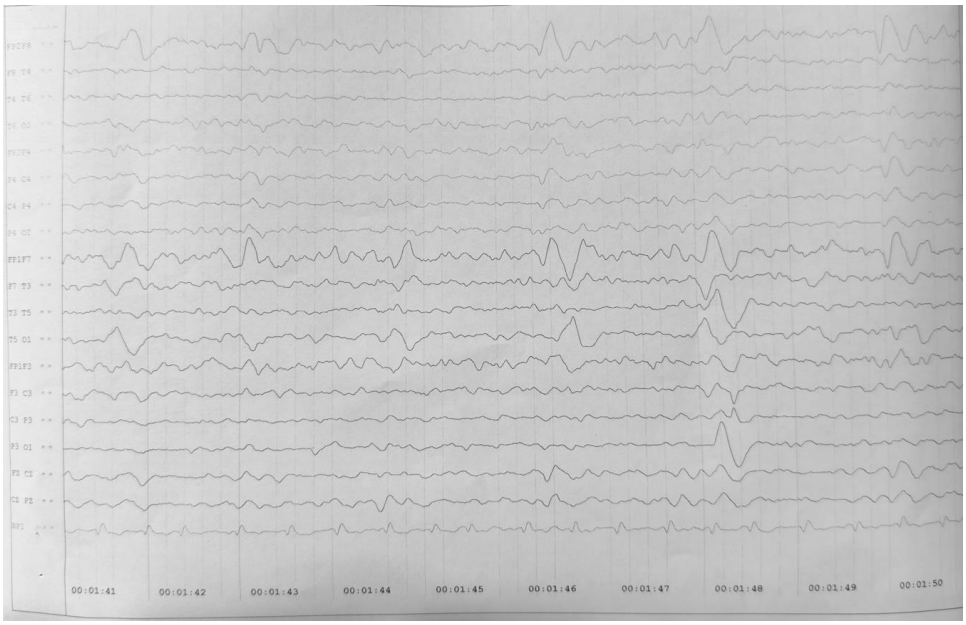

Figure 4: Portable electroencephalography tracing (10–20 montage, bipolar longitudinal) demonstrating frequent left fronto-temporal and right frontal sharp and slow wave discharges superimposed on a symmetrical generalized theta background, consistent with type 1 antibiotic-associated encephalopathy.

DISCUSSION

This case illustrates that Cefepime-induced neurotoxicity can occur despite preserved renal function (serum creatinine 0.4–0.6 mg/dL) when multiple non-renal risk factors converge. The temporal association between Cefepime initiation

and progressive neurological decline within 48–72 hours is consistent with the median latency of 2–5 days reported in systematic reviews.[1,3]

Cefepime crosses the blood–brain barrier and exerts neurotoxicity via concentration-dependent competitive antagonism of $GABA_A$ receptors.[5] Sugimoto *et al.* (2003) demonstrated that Cefepime's 2-aminothiazolyl group confers the highest $GABA_A$ receptor binding affinity among cephalosporins.[5] While renal impairment is the strongest predictor (present in 80–90% of cases), 10–20% of cases occur with preserved renal function.[3,4] Our patient had multiple non-renal risk factors: advanced age (76 year which exceeding the median age of 66–69 years in all major case series [1,3,4,8]); hypoalbuminemia (2.5 g/dL, increasing the unbound Cefepime fraction[6]); sepsis-related blood–brain barrier disruption (progressive leukocytosis and high Procalcitonin[2]); chronic hyponatremia potentially lowering the seizure threshold[7]; and may be presence of incidental calcified meningioma.

The EEG findings of focal epileptiform discharges with generalized theta slowing are consistent with the type 1 pattern of antibiotic-associated encephalopathy.[7] This can be distinguished from hypoxic–ischaemic encephalopathy, which characteristically produces burst-suppression, generalized suppression, or alpha coma.[7] In the systematic review by Payne *et al.* systematic electroencephalographic findings included generalized periodic discharges in 38.7%, epileptiform activity in 28.5%, and diffuse slowing in 19.8%.[1]

Application of the Bradford Hill criteria[10] supports a probable causal relationship: temporality (onset within 48–72 hours[3]); biological plausibility ($GABA_A$ antagonism amplified by non-renal factors[5]); consistency (reproduced across multiple systematic reviews[1,3,4]); coherence (type 1 EEG pattern[7]); and analogy (recognised class effect across beta-lactams.[9]) The reversibility criterion is not assessable because as the patient died over next 3 days and hence precluded formal dechallenge also. Though reversibility is reported in 80–87% of published cases[3,4] but unfortunately our patient did not survive. Boschung-Pasquier *et al.* (2020) identified a trough concentration threshold of 7.7 mg/L (sensitivity 68%, specificity 79%), with levels above 20 mg/L associated with fivefold increased risk.[6] Maan *et al.* (2022) reported that 93.3% of 291 patients presented with altered mental status, with a median latency of 4 days.[3] The Fugate *et al.* (2013) prospective evaluation found neurotoxicity in 15% of 100 critically ill patients at standard dosing.[8]

Limitations

Serum Cefepime trough levels were not measured. The concurrent use of Cefepime–enmetazobactam rather than Cefepime monotherapy introduces uncertainty, though enmetazobactam is not known to alter Cefepime central nervous system penetration. While serum creatinine remained normal, the possibility of subclinical acute kidney injury cannot be excluded; creatinine is a lagging biomarker with a recognised lag phenomenon, and cystatin C levels were not available at our institution.

FINAL DIAGNOSIS

Cefepime-induced neurotoxicity with preserved renal function, complicated by sepsis.

STATEMENT OF CLINICAL SIGNIFICANCE

This case demonstrates that Cefepime-induced neurotoxicity can occur despite preserved renal function when non-renal risk factors—advanced age, hypoalbuminemia, sepsis-related blood–brain barrier disruption, and chronic electrolyte disturbance—converge. Cefepime-induced encephalopathy can follow a fulminant course, with progressive decline in

consciousness. Clinicians should maintain a high index of suspicion in at-risk patients regardless of renal function status, obtain early electroencephalography when Cefepime-induced neurotoxicity is suspected. Promptly discontinue Cefepime with transition to an alternative antimicrobial agent. Therapeutic drug monitoring targeting trough levels below 20 mg/L may guide dose adjustment in patients with multiple risk factors.

PATIENT CONSENT

Written informed consent for publication of this case report and accompanying images was obtained from the patient's next of kin.

ETHICS APPROVAL

Ethical approval was waived because this study described a single anonymized case report.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

SOURCE OF SUPPORT

Nil

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