Cefepime Induced Neurotoxicity Mimicking Clinical Presentation of Left Middle Cerebral Artery Infarction: A Case Report and Review of Literature

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Abstract

Purpose: Cefepime is a widely used antibiotic which was known to have neurotoxicity resulted from its ability to cross the blood-brain barrier and a wide variety of symptoms had been documented. Here we reported a case of Cefepime induced neurotoxicity with rare presentation. The aim of this study was to improve the knowledge of this condition.

Case Report: A 89-year-old female with a history of ESRD (end stage renal disease) and superimposed acute cholecystitis was treated with Cefepime. She developed the symptoms of global aphasia, right hemiplegia, leftward eye deviation and abnormal plantar reflex at right foot, which resembled acute ischemic stroke at left MCA (middle cerebral artery), on the fourth day of Cefepime treatment. There was no evidence of acute infarction in MRI (magnetic resonance imaging) of brain and EEG (electroencephalography) revealed NCSE (nonconvulsive status epilepticus). NCSE was suspected to be attributed to Cefepime-induced neurotoxicity. The patient's main risk factors were decreased renal clearance and incorrect dosing.

Conslusion: Cefepime-induced neurotoxicity should be suspected in patients who developed neurologic symptoms after the administration of Cefepime. Emergent image study for excluding more commonly seen or critical etiologies and further evaluation with EEG were necessary. For those patients who have risk factors for Cefepime neurotoxicity, such as ESRD, TDM (therapeutic drug monitoring) may be useful in providing close monitoring and preventing adverse effects associated with Cefepime treatment.

Keyword: Cefepime, acute ischemic stroke, aphaia, nonconvulsive status epilepticus.

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INTRODUCTION

Cefepime is a broad-spectrum, fourth-generation cephalosporin which was known to have neurotoxicity resulted from its ability to cross the blood-brain barrier. Documented symptoms include conscious disturbance, encephalopathy, myoclonus, seizure, and aphasia. Risk factors of neurotoxicity include renal dysfunction,

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excessive dosing, preexisting brain injury, and elevated serum Cefepime concentrations[1]. Here we reported a case of Cefepime induced neurotoxicity mimicking symptoms of acute left MCA (middle cerebral artery) infarction in an ESRD (end stage renal disease) patient.

CASE PRESENTATION

A 89-year-old, right-handed woman with the history of hypertension, type 2 diabetes mellitus, ESRD and choledolithiasis developed acute cholecystitis. Cefepime treatment was started at a dose of 1g every 12 hours. On the third day of Cefepime treatment, the patient's consciousness was clear but the patient presented right hemiplegia and aphasia on the fourth day of Cefepime treatment. Neurologist was consulted and neurological examinations revealed global aphasia, dysphagia, right hemiplegia, symmetric deep tendon reflex, leftward eye deviation with preserved oculocephalic reflex and abnormal plantar reflex at right foot. Her mental status was mildly drowsy and she did not have any convulsive movements. There was no intracranial hemorrhage but multiple old infarctions and arteriosclerosis in CT (computed tomography) of brain and no apparent

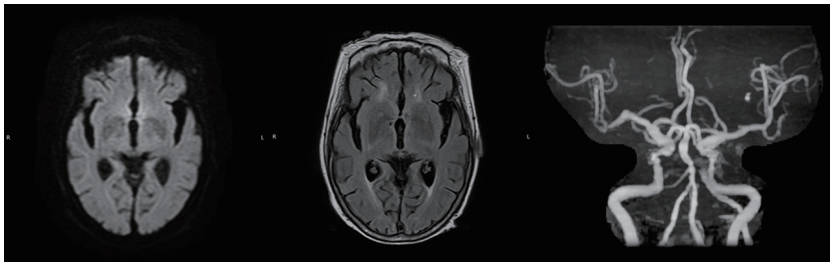

Figure 1. Presence of some tiny hyperintensities on T2 FLAIR image in the periventricular and subcortical white matter region but no hyperintensities on Diffusion-weighted images. There was no occluded vessel noted in Magnetic Resonance Angiography

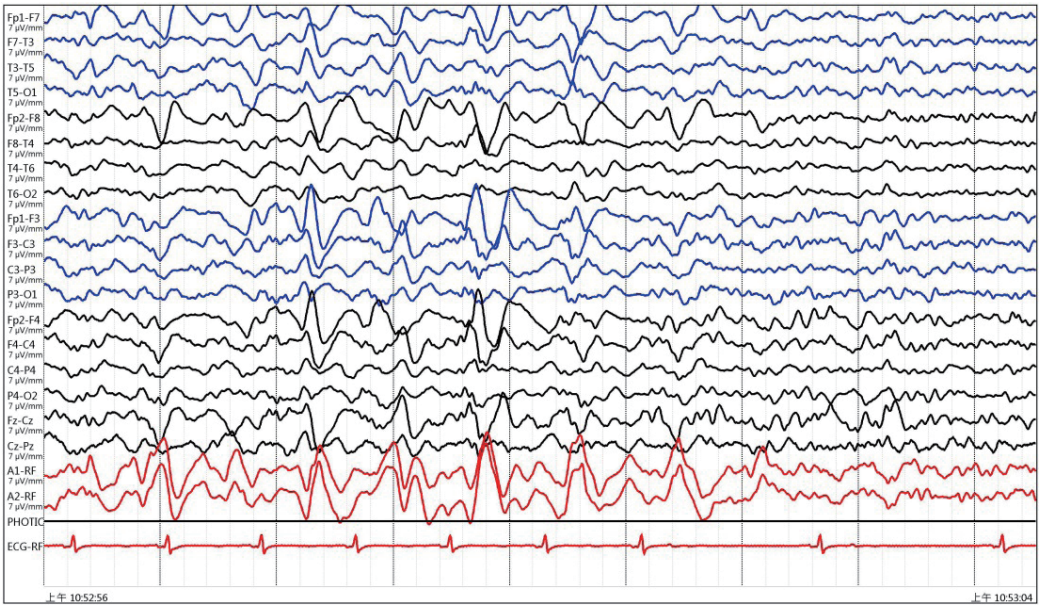

Figure 2. This EEG tracing was composed by diffuse background slow wave and minor diffuse beta activity. There was intermittent delta activity over left temporal region. Sharp and wave complexes can be idntified with its max. on electrode F3,F7. Indicating focal irritability with underlying cortical dysfunction.

metabolic abnormality in blood test. Acute ischemic stroke at left MCA territory was suspected initially due to acute time course and multiple risk factors. Thus antiplatelet was prescribed for secondary stroke prevention. However, there was no evidence of acute infarction in MRI (magnetic resonance imaging) of brain but only an old infarction over right basal ganglia (Figure 1). EEG (electroencephalography) was performed and revealed diffuse cortical dysfunction with focal epileptogenicity on the left frontal-temporal region, sharp and wave complexes can be identified with its max on electrode F3, F7 (Figure 2). Aphasic status epilepticus was suspected by clinical symptoms and EEG result. We also noticed that the dosage of Cefepime was not appropriately reduced based on her renal function. We then considered Cefepime-induced neurotoxicity to be the possible cause of aphasic status epilepticus. We tapered down the dosing of Cefepime to 1g daily from the sixth day of treatment. After dosage adjustment and regular hemodialysis, her aphasia and hemiplegia gradually improved and the abnormal plantar reflex also diminished. She totally recovered from the symptoms 7 days after we adjusted the dose.

DISCUSSION

β-lactam antibiotics, such as cephalosporins and penicillins, had been reported to be proconvulsive via inhibition of GABAA-mediated neurotransmission. These antibiotics block GABAA receptor-mediated inhibitory responses by competitively inhibiting GABA-induced Cl– currents, which leads to depolarization of the postsynaptic membrane potential and results in epileptogenicity [(2)].

The neurotoxicity of Cefepime, including reducing seizure threshold, is usually associated with decreased Cefepime clearance that resulting from reduced glomerular filtration[(3)]. A systemic review published in 2017 reported 135 cases of Cefepime-induced neurotoxicity and documented symptoms included reduced consciousness (47%), myoclonus (42%), confusion (42%), aphasia (15%), seizures (13%), and agitation (11%). The median onset of neurotoxic effect from initiation of Cefepime was 4 days. Furthermore, all patients who underwent electroencephalogram (73%) demonstrated abnormalities[(1)]. The most common EEG pattern was generalized periodic discharge with or without triphasic morphology, followed by generalized rhythmic delta activity and generalized spike-and-waves. The diagnosis of Cefepime-induced neurotoxicity should base on the temporal association between either neurologic symptoms and administration of Cefepime or clinical/EEG improvements and discontinuation of Cefepime[(4)].

Higher plasma trough concentrations of Cefepime were significantly associated with risk of neurotoxicity thus discontinuation or reduction in dose of the drug are necessary and hemodialysis is sometimes needed[(5)]. Clinical improvement was observed a median of 2 days after management in a systemic review, which was compatible with our case[(1)]. A retrospective cohort study in 2020 concluded that therapeutic drug monitoring (TDM) should be systematically used to reduce the dose of Cefepime in patients with risk factors for Cefepime neurotoxicity, aiming at trough concentrations <7.5 mg/L[(5)]. However, the technique is not routinely performed in Taiwan.

Non-convulsive status epilepticus (NCSE) is defined as either status epilepticus without prominent motor symptoms more than 10 minutes or multiple non-convulsive seizure activity without full recovery of consciousness between attacks. It could present with a wide variety of unspecific symptoms thus it is not able to be diagnosed from clinical signs alone. Aphasia may present as a symptom of seizure and aphasic SE has been included in the category of NCSE and sub-classified in focal SE[(6)]. In such cases, it is crucial to exclude more commonly seen or critical etiologies, including acute cerebrovascular accident.

We presented a case of a 89-year-old female with a history of ESRD and superimposed acute cholecystitis which treated with Cefepime. She developed the symptoms of global aphasia, right hemiplegia, and abnormal plantar reflex at right foot, which resembled acute ischemic stroke at left MCA but eventually found to be NCSE attributed to Cefepime. The patient's main risk factors were decreased renal clearance and incorrect dosing. Various neurological symptoms were reviewed in literature on this topic but only a few case reports documented Cefepime induced neurotoxicity that mimicking clinical presentation of acute ischemic stroke[(7, 8)]. The documented cases presented similar clinical features and EEG pattern, despite age and gender, under the scenario of renal function impairment

Table 1. Comparison of the patients with stroke-mimicking Cefepime induced neurotoxicity in recent documented case reports

		Kwon, J., et al. (2014)	Cunningham, J. M., et al. (2020)	Presented case
Age (y/o)		36	72	89
Sex		male	female	female
Clinical presentation	Eye sign	?	?	+
	Hemiplegia/hemiparesis	+	+	+
	Aphasia	+	+	+
	Plantar reflex	?	-	+
	Convulsive movements	-	-	-
Underlying medical history,		Nephrotic syndrome, UTI	HTN, insulin dependent DM, a prior history of CAD, pelvic osteomyelitis	HTN, type 2 DM, ESRD, cholecystitis
Renal function impairment		+, CCr: 49 mL/min/1.73 m^2, calculated by MDRD formula	+, CCr: 45ml/min, calculated by modified Cockcroft-Gault formula	+, under hemodialysis
EEG finding		continuous 2–3 Hz rhythmic spike-and-waves in left hemisphere	bi-frontal predominant, 1.5 to 2.5 Hz rhythmic spike and wave pattern	intermittent delta activity over left temporal region, sharp and wave complexes on electrode F3,F7
Dosing of Cefepime		2 grams IV Q8H	2 grams IV Q8H	1gram IV Q12H
If the symptoms subsided after discontinuation or dose adjustment of cefepime		Yes	Yes	Yes

Note. += positive; -= negative; ?= not documented; UTI= urinary tract infection; HTN= hypertension; DM= diabetes mellitus; CAD= coronary artery disease; CCr= creatinine clearance; IV= intravenous; Q8H= every 8 hours; Q12H= every 12 hours

with incorrect dose of Cefepime. (Table 1)

CONCLUSION

This is a typical case with rare presentation, which may lead to delays in diagnosis. Emergent image study for excluding more commonly seen or critical etiologies and further evaluation with EEG were necessary. For those patients who has risk factors for Cefepime neurotoxicity, such as ESRD, TDM may be useful in providing close monitoring and preventing adverse effects associated with Cefepime treatment.

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