Cefepime-Induced Encephalopathy in a Tertiary Medical Center in Korea

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Background and Purpose Cefepime is a widely used fourth-generation cephalosporin. It is commonly used as a first-line antibiotic to treat various infectious diseases such as hospital-acquired pneumonia, urinary tract infections, and bacterial meningitis. The primary outcome of this study was the development of cefepime-induced encephalopathy (CIE) at a tertiary medical center in Korea. We also aimed to describe the clinical features of CIE.

Methods We enrolled 1,793 consecutive patients treated with cefepime. The CIE group included 44 patients who experienced altered consciousness after receiving cefepime without any other obvious cause and showed full recovery after stopping cefepime. This study collected demographic data, laboratory findings, and clinical data including the cause of infection, duration for onset of altered consciousness, duration of cefepime treatment, dosage of cefepime, duration of recovering consciousness after stopping cefepime, sequelae after encephalopathy, and electroencephalography data.

Results Forty-four (2.5%) patients were included in the CIE group. The age was significantly higher in the CIE group than in the control group (71.2±10.8 years vs. 64.7±16.1 years, mean± standard deviation; p=0.007), and females constituted a significantly large proportion in the CIE group (27 of 44, 61.4%). The CIE group had higher blood urea nitrogen (34.7±22.6 mg/dL vs. 23.0±17.5 mg/dL, p<0.001) and creatinine (2.2±2.5 mg/dL vs. 1.1±1.3 mg/dL, p<0.001), and lower estimated glomerular filtration rate (eGFR) (56.3±46.0 mL/min/1.73 mm² vs. 98.8±66.3 mL/min/1.73 mm², p<0.001). Multivariate analysis showed that only eGFR was significantly related to CIE.

Conclusions The incidence of CIE was 2.5% in this study. It is essential to consider the possibility of CIE occurring, especially in patients with lower values of eGFR and dialysis.

Key Words encephalopathy, cefepime, epilepsy, incidence, electroencephalography.

INTRODUCTION

Cefepime is a widely used fourth-generation cephalosporin. It is commonly used as a first-line antibiotic to treat various infectious diseases such as neutropenic fever, urinary tract infections, hospital-acquired pneumonia, bacterial meningitis, and skin, intra-abdominal, and gynecological infections.[1] The clinical features of cefepime-induced encephalopathy (CIE) are confusion, agitation, myoclonic jerks, epileptic seizures, coma, and convulsive status epilepticus.[2] CIE was recently classified as a type-1 antibiotic-associated encephalopathy (AAE).[3] In type-1 AAE, seizures are observed more frequently than in psychosis. Predisposing factors for CIE include a high cefepime dosage, reduced drug renal clearance, and older age.[4-6]

The reported incidence of CIE has ranged from 0.2% to 7.0%.[2,7-9] Appa et al.[2] reported an incidence at their center of 1 (0.2%) in 480 courses of cefepime. Naeije et al.[7] reported

that 14 (1.25%) out of 1,120 patients who received cefepime showed continuous or intermittent generalized periodic epileptiform discharges. Fugate et al.[9] found that 7 of 100 patients in an intensive care unit (ICU) setting had definite CIE. In Korea, Kang and Kim[8] reported that 21 (0.85%) of 2,461 patients were diagnosed with CIE. This wide range of the reported incidence rates may be expected given both the heterogeneity in diagnostic criteria for CIE and the diversity of the populations analyzed in these studies.

In this study we aimed to 1) determine the single-center incidence of CIE in Korea, 2) describe the clinical characteristics of CIE, and 3) identify the potential risk factors for CIE.

METHODS

Subjects

We selected consecutive patients diagnosed with an infectious disease and treated with cefepime at the Dongsan Medical Center in Korea from January 2013 to March 2015. The included patients were aged 18–80 years and first-time users of cefepime for an infectious condition. The following exclusion criteria were applied: 1) altered consciousness at the start of cefepime treatment, 2) neurological deficits or psychiatric disorders, 3) development of an altered consciousness due to other conditions such as mental retardation or alcohol or drug abuse, or 4) received antiepileptic drug treatment for epilepsy or seizure within the previous year. After applying the exclusion criteria, 1,802 patients were enrolled. The study was approved by the Institutional Review Board of the Dongsan Medical Center (IRB No. 2015-11-020).

Data collection

We defined the CIE group as patients who fulfilled the following criteria: 1) altered consciousness, hallucinations, behavior change, myoclonus, or seizure after receiving cefepime, 2) neurological alteration not due to any other cause such as central nervous system deficit, delirium, psychosis, or metabolic cause, 3) experienced neurological alterations but recovered within a few days after stopping cefepime and subsequently fully recovered their consciousness to the premorbid state, and 4) all of the aforementioned criteria confirmed by a neurologist or their own physician. Neurologists reviewed all medical records to include patients with newly developed acute neurological deterioration or expressed altered levels of consciousness during cefepime treatment. Patients who died during cefepime treatment or after stopping cefepime were excluded.

Demographic and laboratory findings were collected at the beginning of cefepime treatment. The demographic data included age, sex, and laboratory findings such as white blood cells, red blood cells, platelets, hemoglobin, electrolytes, blood sugar, liver enzymes, bilirubin, albumin, blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP), and erythrocyte sedimentation rate. The data related to clinical mental status included the score on the modified Rankin Scale during cefepime treatment, whether patients developed an altered consciousness after using cefepime, the duration for onset of altered consciousness after using cefepime, the duration of recovering consciousness after stopping cefepime, the severity of the altered consciousness according to the Glasgow Coma Scale score, and the presence or absence of seizures. The data related to infection included the duration of cefepime treatment, the dosage of cefepime, the duration of recovering consciousness after stopping cefepime, and the reasons for cefepime treatment such as community-acquired pneumonia, hospital-acquired pneumonia, urinary tract infection, colitis, or neutropenic fever. If seizures occurred, data including the type of seizures, the number of seizures, and the presence of generalized tonic–clonic seizure were collected. Additionally, outcome-related data such as survival or death and sequelae of CIE were collected. The electroencephalography (EEG) data of the CIE group recorded during the encephalopathy episode were reviewed by an epilepsy specialist.

Statistical analyses

Continuous variables are presented as number and frequency or mean±standard-deviation values. We also conducted a series of internal subgroup comparisons of nominal variables using the chi-squared test, and analyzed the continuous variables using analysis of variance or the independent t-test. A probability value of $p < 0.05$ was considered statistically significant.

To identify the factors contributing to CIE development, data analysis was performed for score derivation based on univariate and multivariate logistic regressions. All statistical analyses were performed using IBM SPSS Statistics (version 21.0, IBM Corp., Armonk, NY, USA).

RESULTS

Subject characteristics and factors correlated with the CIE group

Nine of the 1,802 recruited participants were excluded. Eight out of the nine excluded patients showed altered consciousness after cefepime use but did not recover within a few days after stopping cefepime. An underlying severe infectious conditions or metabolic encephalopathy were possible explanations for the altered consciousness. One patient died of an

unknown cause during cefepime use. Forty-four (2.5%) of the 1,793 finally enrolled patients showed an altered consciousness during cefepime treatment and recovered after stopping cefepime, and were thus included in the CIE group. The remaining 1,749 (97.5%) patients showed no alteration of their consciousness during cefepime treatment.

The age was significantly higher in the CIE group (71.2±10.8 years, p=0.007) than in the control group (64.6±16.1 years). Females constituted a significantly larger proportion of patients in the CIE group (27 of 44, 61.4%) than in the control group (773 of 1,749, 44.2%). The daily dosage of cefepime and the duration of cefepime treatment did not differ significantly between the two groups. However, the proportion of subjects receiving cefepime doses that were higher than that specified in the Food and Drug Administration standard was higher in the CIE group than in the control group (31.8% vs. 8.5%, p<0.001).

The laboratory findings revealed that the CIE group had higher BUN (34.7±22.6 mg/dL vs. 23.0±17.5 mg/dL, p<0.001), higher creatinine (2.2±2.5 mg/dL vs. 1.1±1.3 mg/dL, p<0.001), and lower estimated glomerular filtration rate (eGFR) (56.3±46.0 mL/min/1.73 mm^2 vs. 98.8±66.3 mL/min/1.73 mm^2, p<0.001) than the control group. The proportion

of patients with eGFR above 60 mL/min/1.73 mm^2 was significantly higher in the control group than in the CIE group (77.5% vs. 36.4%, p<0.001). The CRP, hemoglobin count, and platelet count did not differ significantly between the groups (Table 1).

In a univariate analysis and a reanalysis using multivariate logistic regression for investigating the factors contributing to the development of CIE, only eGFR showed a significant correlation with CIE (p=0.003). The other variables of age, sex, and CRP, BUN, and creatinine levels showed no significant correlation with CIE in the multivariate logistic regression analysis (Table 2).

Clinical characteristics in the CIE group

Among 44 (2.5%) of the 1,793 patients in the CIE group, 20 (45.4%) had hypertension and 11 (25.0%) had diabetes mellitus. Ten (22.7%) patients suffered from chronic renal failure, of which three underwent hemodialysis, one underwent peritoneal dialysis, and the others had not received dialysis when the study was conducted. No patient had a previous diagnosis of epilepsy or encephalitis. Seventeen (38.6%) and two (4.5%) patients received cefepime to treat respiratory and urinary tract

Table 1. Comparison of the CIE and control groups

	CIE n=44 (2.5%)	Controls n=1,749 (97.5%)	p
Age, years	71.2±10.8	64.6±16.1	0.007*
Sex, female	27 (61.4)	773 (44.2)	0.026*
Hypertension	20 (45.4)	623 (35.6)	0.182
Diabetes mellitus	11 (25.0)	410 (23.4)	0.916
Previously diagnosed CRF	10 (22.7)	114 (6.5)	<0.001*
CRF without dialysis	6	82	
Hemodialysis	3	22	
Peritoneal dialysis	1	6	
Renal transplantation	0	4	
Duration of cefepime treatment, days	8.4 [2–23]	7.5 [1–49]	0.296
Dosage of cefepime, mg/day	4,034±1,679	4,282±1,375	0.256
Dosage of cefepime higher than the FDA standard	14 (31.8)	148 (8.5)	<0.001*
Modified Rankin Scale score	3.7±1.4	1.5±1.7	0.507
Laboratory findings			
Hemoglobin, g/dL	10.2±2.5	10.8±2.2	0.066
Platelets, μL (×10^3)	169.3±132.6	207.8±147.0	0.075
BUN, mg/dL	34.7±22.6	23.0±17.5	<0.001*
Creatinine, mg/dL	2.2±2.5	1.1±1.3	<0.001*
eGFR, mL/min/1.73 mm^2	56.3±46.0	98.8±66.3	<0.001*
Baseline eGFR ≥60 mL/min/1.73 mm^2	16.0 (36.4)	1,356.0 (77.5)	<0.001*
CRP, mg/dL	11.9±8.8	8.5±8.4	0.450

Data are n (%), n, mean±standard-deviation, or mean [range] values.
*Statistical significance (p<0.05).
BUN: blood urea nitrogen, CIE: cefepime-induced encephalopathy, CRF: chronic renal failure, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, FDA: Food and Drug Administration.

Table 2. Results from the multivariate logistic regression analysis of cefepime-induced encephalopathy

	Beta	Odds ratio	p	95% confidence interval	
				Low	Upper
Age	0.024	1.025	0.072	0.998	1.052
Sex	0.527	1.695	0.101	0.902	3.185
CRF	0.285	1.329	0.316	0.762	2.319
BUN	0.000	1.000	0.981	0.983	1.017
Creatinine	0.020	1.020	0.862	0.816	1.275
eGFR	-0.018	0.983	0.003*	0.971	0.994

Age, Sex, eGFR and CRF were considered independent variables.
*Statistical significance ($p<0.05$).
BUN: blood urea nitrogen, CRF: chronic renal failure, eGFR: estimated glomerular filtration rate.

infections, respectively.

During cefepime treatment, 16 (36.4%) patients suffered from confusion, 15 (34.1%) from drowsiness, 9 (20.5%) from stupor, and 4 (9.1%) were semicomatose or comatose. Patients began to show symptoms of altered consciousness within a mean of 3.6 days after antibiotic administration. The duration of an altered consciousness was 3.8±1.6 days, and the duration of cefepime treatment was 8.4±5.5 days (range=2−23 days). Four (9.1%) patients suffered clinical seizures and three were diagnosed with status epilepticus. During encephalopathy, four (9.1%) patients experienced dysarthria and one (2.3%) suffered from aphasia. The recovery of consciousness to premorbid levels took more than 1 week in 56.8% of the patients, whereas this happened immediately after stopping cefepime in 34.1% of them. Twenty-one (47.7%) patients survived, while 25 (52.3%) died due to infections or comorbidities (Table 3).

The overall incidence of CIE was 2.5%, but this was much higher in the dialysis patients (12.5%).

CIE occurred in about 1.1% of patients who did not receive dialysis, and eGFR was within the normal range (>60 mL/min/1.73 mm^2). The incidence of CIE among subjects with eGFR below 60 mL/min/1.73 mm^2 was 63.6%. CIE developed in 12.4% of the patients with eGFR below 30 mL/min/1.73 mm^2 but more than 11 mL/min/1.73 mm^2, in 4.8% of the patients with eGFR below 11 mL/min/1.73 mm^2, and in 4.0% of the patients with eGFR not more than 60 mL/min/1.73 mm^2 but 30 mL/min/1.73 mm^2 or more (Table 4).

EEG findings in the CIE group
Thirty of the 44 CIE patients underwent an EEG examination at that time of altered consciousness. Eight of these patients showed 2-Hz generalized periodic discharges (GPDs) with triphasic morphology, two of which had continuous 2- to 3-Hz GPDs with triphasic morphology and were diagnosed with nonconvulsive status epilepticus. The remaining six patients had occasional GPDs with triphasic morpholo-

gy. Ten out of 30 patients who underwent EEG showed continuous slow theta activity in the background, while 8 showed a slowing of delta to theta activity with triphasic morphology. Two patients had normal EEG findings, one showed background suppression without reactivity, and one showed frontal intermittent rhythmic delta activity. Below we describe the clinical features and EEG characteristics of two representative cases.

Representative case 1
A 66-year-old woman who had chronic kidney disease with peritoneal dialysis was diagnosed with peritoneal dialysis-related peritonitis and admitted to the department of nephrology. She was treated with 1-g cefepime once daily, and the peritoneal device was removed. After 4 days she developed confusion, disorientation, and irritability. A neurological examination revealed that the patient was confused but fully oriented. EEG showed continuous frontally predominant 1-Hz GPDs with triphasic morphology and background theta slowing (Fig. 1A).

The neurologist immediately instructed the physician to stop cefepime. She recovered consciousness at 6 hours after stopping cefepime, and returned to her normal appearance after 1 day. In the follow-up EEG, the continuous theta slowing persisted but the epileptiform discharges had disappeared (Fig. 1B), and so the diagnosis of CIE was confirmed. All of the symptoms improved after replacing cefepime with ceftriaxone and clindamycin, and the patient was discharged without any complications.

Representative case 2
A 74-year-old woman with chronic kidney disease visited the emergency room with cough, dyspnea, and palpitation. She had been receiving on hemodialysis for 19 years. She was diagnosed with pneumonia and treated with empirical antibiotics (2-g cefepime once after hemodialysis). After 3 days she developed confusion, insomnia, and irritability, and 2 days

later her treating physicians made an emergency call to a neurologist after she fell into a stupor. A neurological examination revealed that she exhibited stupor with intact oculocephalic and pupil reflexes. Her power of all major joints were 3/5 of medical research council grade, and her sensory function for painful stimulation was intact all over the body. Brain magnetic resonance imaging did not reveal any acute destructive lesion. EEG showed continuous 3-Hz GPDs (Fig. 2A).

Table 3. Clinical characteristics in the cefepime-induced encephalopathy group

Characteristic	Value (*n*=44)
History of epilepsy or encephalitis	0 (0.0)
Reason for cefepime use	
Respiratory infection	17 (38.6)
Urinary tract infection	2 (4.5)
Other infections	25 (56.8)
Altered consciousness during cefepime use	
Confusion	16 (36.4)
Drowsiness	15 (34.1)
Stupor	9 (20.5)
Semicomatose or comatose	4 (9.1)
Duration of altered consciousness	
<1 day	7 (15.9)
1–2 days	3 (6.8)
3–7 days	16 (36.4)
8–10 days	18 (40.9)
Duration for onset of altered consciousness, days	3.6 [0–17]
Clinical seizure	
No clinical seizure	40 (90.9)
Complex partial seizure	1 (2.3)
Generalized tonic–clonic seizure	1 (2.3)
Unknown	2 (4.5)
Status epilepticus (*n*=43)	
Convulsive	1 (2.3)
Nonconvulsive	2 (4.7)
Focal neurological deficit	
No deficits	39 (88.6)
Dysarthria	4 (9.1)
Aphasia	1 (2.3)
Duration of cefepime use, days	8.4±5.5
Duration of altered consciousness, days	3.8±1.6
Duration of fully recovering consciousness after stopping cefepime	
Immediately	15 (34.1)
<3 days	2 (4.5)
3–7 days	2 (4.5)
>7 days	25 (56.8)
Mortality status	
Survived	21 (47.7)
Died	23 (52.3)

Data are *n* (%), mean±standard-deviation, or mean [range] values.

The neurologist diagnosed her with nonconvulsive status epilepticus due to CIE. The patient was administered 2 mg of lorazepam, but the GPDs persisted (Fig. 2B). This was followed by 3,000 mg of intravenous levetiracetam, and cefepime was replaced with levofloxacin. She was transferred to the department of neurology and EEG monitoring was started in the ICU. The epileptiform discharges disappeared after the levetiracetam infusion. She gradually recovered her consciousness and returned to her normal appearance after 5 days. At the end of the EEG monitoring, slow background activity without epileptiform discharges was observed (Fig. 2C). The patient recovered her usual appearance and was discharged on levetiracetam at 1,500 mg twice daily.

DISCUSSION

The present study found that the overall incidence of CIE in patients receiving cefepime in a single tertiary hospital was 2.5%. This is higher than in previously reported studies, with the exception of Fugate et al.[9] reporting that CIE was diagnosed in about 7% of patients in the ICU. Most studies have found the incidence of CIE to be around 1%.[2,7,8] Naeije et al.[7] and Kang and Kim[8] reported incidence rates 1.25% and 0.85%, respectively. These discrepancies between studies might be due to the differences in the diagnostic criteria for CIE. The two large case−control studies used specific EEG characteristics as important diagnostic criteria. However, since about half of the patients in the present retrospective study did not undergo EEG while symptoms persisted, we decided to exclude EEG findings from the diagnostic criteria for CIE.

Cefepime is a fourth-generation cephalosporin that is one of the beta-lactam antibiotics with a broad antimicrobial spectrum.[10] Beta-lactam antibiotics enhance glutamate-mediated excitatory neurotransmission and the properties of gamma-aminobutyric acid, resulting in convulsions.[11] Bhattacharyya et al.[3] reported three distinct clinical phenotypes of AAE. Encephalopathy due to cephalosporins and penicillin are commonly accompanied by seizures or myoclonus arising

Table 4. Incidence of CIE according to eGFR

eGFR, mL/min/1.73 mm²	CIE (*n*=44)	Controls (*n*=1,749)	*p*
Dialysis	4 (12.5)	28 (87.5)	–
0 ≤eGFR <11	2 (4.8)	40 (95.2)	<0.001*
11 ≤eGFR <30	13 (12.4)	92 (87.6)	
30 ≤eGFR ≤60	10 (4.0)	240 (96.0)	
eGFR >60	15 (1.1)	1,349 (98.9)	

Data are *n* (%) values.
*Statistical significance (*p*<0.05).
CIE: cefepime-induced encephalopathy, eGFR: estimated glomerular filtration rate.
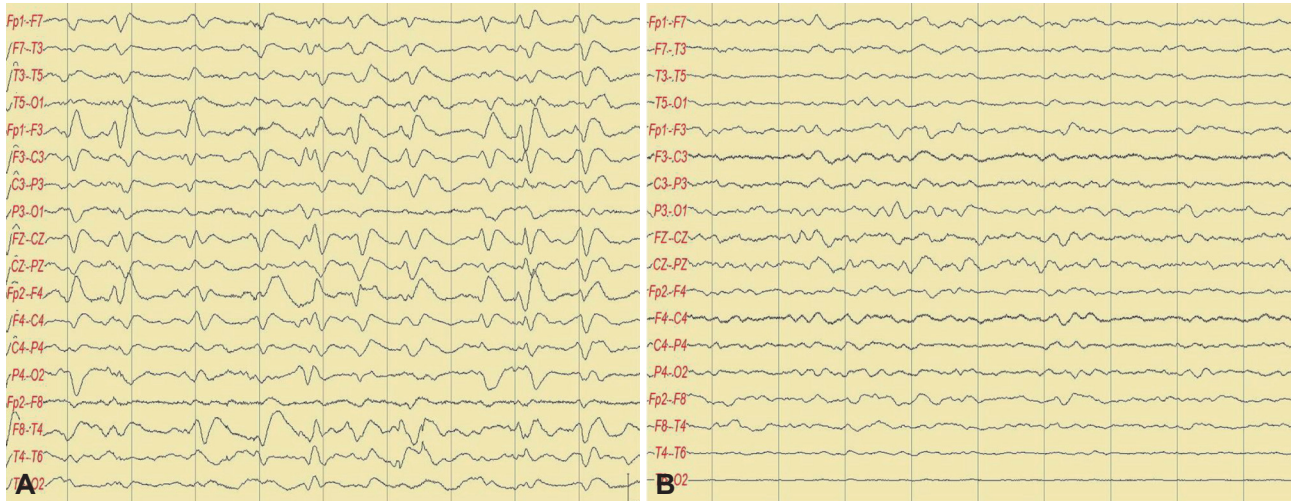
Fig. 1. EEG findings in a patient with cefepime-induced encephalopathy without clinical seizures. A: Continuous frontally predominant 1-Hz generalized periodic discharges with triphasic morphology and background theta slowing were evident during cefepime treatment. B: Follow-up EEG after stopping cefepime showed that continuous theta slowing persisted but epileptiform discharges had disappeared. EEG: electroencephalography.
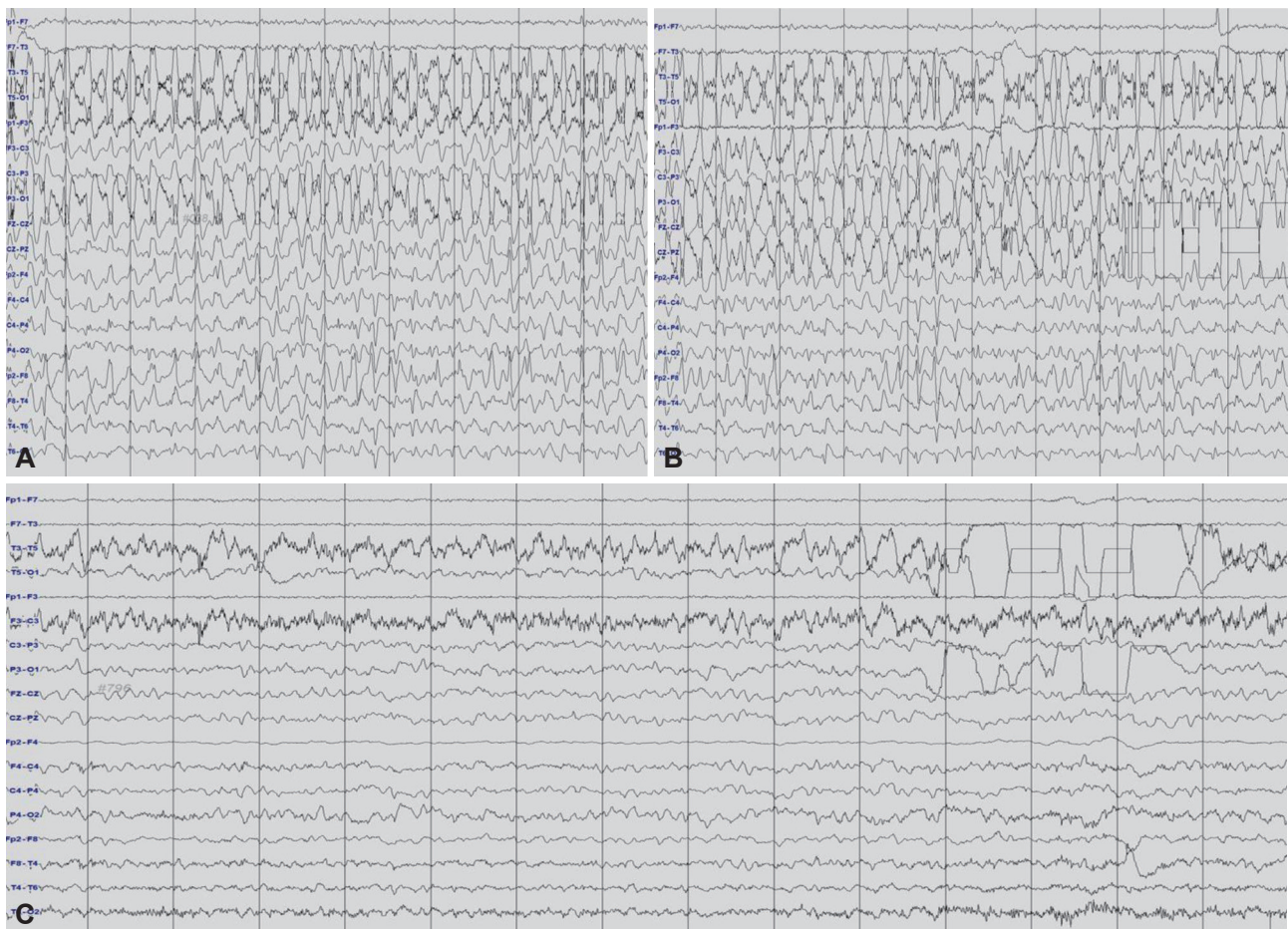

Fig. 2. EEG findings in a cefepime-induced encephalopathy patient with nonconvulsive status epilepticus. A: Continuous 3-Hz GPDs and its evolution.* B: Despite injecting 2 mg of lorazepam, the GPDs persisted.* C: After administering 3,000 mg of levetiracetam intravenously, and followed by cefepime replacement with levofloxacin, background theta-to-alpha slow activity without epileptiform discharges was observed. *The EEG records contain large numbers of artifacts since the electrodes were attached by inexperienced residents of neurology under emergency situations. EEG: electroencephalography, GPDs: generalized periodic discharges.

within days after administration. In this study, 9.1% of the CIE patients suffered clinical seizures, of which 8% were diagnosed as status epilepticus. EEG in the CIE group revealed that 26.7% showed GPDs with a triphasic morphology. These EEG findings were similar to those of several previous case reports. Many case reports have found that the EEG patterns in patients with CIE included rhythmic triphasic waves that were nonreactive to stimulation,[5,6,12,13] nonconvulsive status epilepticus with generalized spikes, and slow-wave or sharp and slow-wave activity.[6,14]

Johnson et al.[15] reported a case having normal renal function with CIE showing stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs). However, our patients with CIE did not show SIRPIDs. Though many studies have found GPDs in EEG during CIE, some have also found various EEG patterns including nonspecific findings or diffuse triphasic waves with generalized slowing only in CIE patients.[16] EEG patterns vary according to the severity of encephalopathy and the timing of the EEG study. In the present retrospective study, we did not include the EEG characteristics in the diagnostic criteria of CIE due to the low rate and varying time points of EEG being performed. Nevertheless, we believe that identifying and reporting various EEG patterns in CIE is valuable, and so consider that further prospective studies are needed.

Cefepime is largely excreted via the kidney, with 85% of the drug excreted in an unchanged form in the urine. The remainder is metabolized by the body to N-methylpyrrolidine and a 7-epimer isomer. This study found that decreased eGFR was the most-significant risk factor for CIE. We showed that lower eGFR levels and dialysis were related to a higher incidence of CIE. We further found that 63.6% of the CIE patients had an eGFR of below 60 mL/min/1.73 mm², which is similar to previous studies.[8] Among patients with reduced renal function who do not receive dialysis, the incidence of CIE was highest when eGFR was above 11 mL/min/1.73 mm² and below 30 mL/min/1.73 mm². Further studies are needed to explain whether the physician had followed the dosing standard according to the eGFR of each patient, and what the serum level of cefepime was for each patient.

Elderly patients show decreased creatinine clearance with age, with the eGFR possibly decreasing to about half its normal value before the serum creatinine level increases to above the upper limit. It is therefore essential to monitor the renal function in elderly patients with severe diseases and sepsis, and in those who are receiving cefepime. In this study we found that those in the CIE group were on average older than controls. However, multivariate analysis revealed that renal function itself is a more-significant risk factor than age.

The present study was subject to a few limitations. Unlike previous studies,[8] we did not include EEG findings in the diagnostic criteria for CIE due to the retrospective design of this study. This might have reduced the specificity of the CIE diagnoses. Furthermore, we did not consider the history of previous seizures or encephalopathy, or the family history of epilepsy. Previous seizures or encephalopathies could significantly influence the EEG patterns of patients and the development of encephalopathy. The estimated incidence of CIE could be lower than the actual incidence since most of the patients receiving cefepime were admitted to the internal medicine department rather than to departments related to neurology. Thus, patients suffering from CIE were easily lost since the physicians might not have considered their altered mental status, and may have inferred that the encephalopathy was due to their poor general condition such as high fever, poor oral intake, malignancy, or sepsis. The lack of further analysis of the causes of delayed recovery and the lack of evaluation for the serum level of cefepime were further limitations.

In conclusion, the overall incidence of CIE was 2.5% in our center. Impaired renal function was the only significant risk factor for CIE. The incidence of CIE was highest (exceeding 12%) in patients receiving dialysis and those with eGFR above 11 mL/min/1.73 mm² but below 30 mL/min/1.73 mm². Caution is needed while prescribing cefepime to such patients. Additional long-term follow-up and prospective studies are needed to evaluate the development of CIE over time and to determine the factors contributing to the development of CIE.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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