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【 CASE REPORT 】

Encephalopathy Induced by High Plasma and Cerebrospinal Fluid Ceftriaxone Concentrations in a Hemodialysis Patient

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Abstract:

Encephalopathy is a rare side effect of cephalosporin treatment. We herein present a case of encephalopathy induced by ceftriaxone, a third-generation cephalosporin, in a patient with renal failure. An 86-year-old woman on maintenance hemodialysis received ceftriaxone for *Helicobacter cinaedi* bacteremia. Her mental status deteriorated during antibiotic treatment, and an electroencephalogram revealed triphasic waves predominantly in the frontal area. Her consciousness improved after the discontinuation of the antibiotic due to the suspicion of ceftriaxone-induced encephalopathy. This is the first reported case of encephalopathy associated with high plasma and cerebrospinal fluid ceftriaxone concentrations, and provides significant evidence for a causal relationship between the administration of ceftriaxone and the onset of encephalopathy.

Key words: ceftriaxone, end-stage kidney disease, encephalopathy, triphasic waves

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Introduction

Encephalopathy is a rare side effect of cephalosporin treatment. Although encephalopathy caused by ceftriaxone, a third-generation cephalosporin, is particularly rare, several studies have reported this complication in patients with end-stage kidney disease (ESKD) (1, 2). Renal insufficiency is considered to be a predisposing factor for ceftriaxone neurotoxicity (1, 2); however, to date, no studies have evaluated the plasma and cerebral spinal fluid (CSF) concentrations of ceftriaxone in relation to encephalopathy. We herein present a case of encephalopathy in a hemodialysis patient who received intravenous ceftriaxone for *Helicobacter cinaedi* bacteremia. Our analysis revealed that the plasma and CSF concentrations of ceftriaxone were higher than the optimal range.

Case Report

An 86-year-old woman on maintenance hemodialysis for ESKD due to benign nephrosclerosis presented to the emergency department with complaints of vomiting, diarrhea, and mild alteration of consciousness. Her medical history included rheumatoid arthritis, hypothyroidism, and hypertension. Her medications included prednisolone (5 mg), levothyroxine, rabeprazole, mosapride, butyric acid bacteria, and amezinium metilsulfate. A physical examination revealed soft abdomen; however, the patient complained of pain in her right lower abdomen. Although laboratory data showed leukocytosis and an elevated C-reactive protein level, the patient was afebrile and hemodynamically stable when she presented to the emergency department. She was sent home without any medication. One day later, she developed high fever with persistent abdominal pain and was admitted to our hospital. Her altered consciousness had im-

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proved at the time of admission. Intravenous ceftriaxone (1 g daily) was administered as an empirical treatment for bacterial enteritis. On the third day of admission, the presence of gram-negative bacteria was confirmed by blood culture, and the ceftriaxone dosage was increased to 2 g daily. Eventually, *Helicobacter cinaedi* was identified as the causative agent by blood culture.

On the 13th day of ceftriaxone treatment, the patient showed an altered mental state and a decreased level of consciousness as well as myoclonic jerks involving the right shoulder and arm. A neurological examination revealed roving eye movement and preserved light reflex. Brain magnetic resonance imaging did not reveal acute stroke or other focal findings that would account for her symptoms. No obvious abnormalities in the liver function or serum electrolyte levels were observed (Table). Hypoglycemia was not detected by capillary glucose monitoring. A CSF analysis revealed no elevated cell counts, and CSF cultures were negative. Electroencephalography (EEG) was performed, which showed generalized triphasic waves (TWs), predominantly in the frontal area (Fig. 1). Because the patient's symptoms were suspected to have been caused by ceftriaxone-induced encephalopathy, ceftriaxone was discontinued on the day after the onset of neurological symptoms. Consequently, a progressive improvement in the patient's neurological state was noted, and her consciousness completely recovered at four days after the discontinuation of ceftriaxone. Accordingly, she was diagnosed with ceftriaxone-induced encephalopathy. EEG performed seven days after the discontinuation of ceftriaxone revealed normal wave patterns and the absence of TWs.

Table. Laboratory Data at the Onset of Neurological Symptoms.

Alb	2.6 g/dL	TSH	5.03 μIU/mL
BUN	26 mg/dL	FT3	1.14 pg/mL
Cr	3.52 mg/dL	FT4	1.25 ng/dL
Na	145 mEq/L	TPO-Ab	9 IU/mL
K	4.6 mEq/L	Vit B1	54 ng/mL
Cl	106 /mEq/L	Vit B12	193 pg/mL
Ca	8.4 mg/dL		
Mg	2.0 mg/dL	WBC	10,700 /μL
Glucose	84 mg/dL	Hb	11.0 g/dL
CRP	0.64 mg/dL	Plt	19.0 /μL
NH3	12 μmol/L		
T-Bil	0.2 mg/dL	Cerebrospinal fluid	
γ-GTP	19 U/L	Cell count	1 cell/μL
AST	15 U/L	Glucose	48 mg/dL
ALT	13 U/L	Protein	64 mg/dL

Alb: Albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Ca: calcium, Cl: chloride, Cr: creatinine, CRP: C-reactive protein, FT3: free triiodothyronine, FT4: Free Thyroxin, γ-GTP: gamma-glutamyltransferase, K: potassium, LDH: lactate dehydrogenase, Mg: magnesium, NH_3: ammonia, Plt: platelet, RBC: red blood cell, T-Bil: total bilirubin, TPO-Ab: thyroid peroxidase antibody, TSH: thyroid-stimulating hormone, Vit B1: vitamin B1, Vit B12: vitamin B12

The differential diagnoses included other potential causes of disturbed consciousness (e.g., electrolyte disorders, metabolic alterations, cerebral hypoxia, infection, stroke, and medication use). However, no other factors that could possibly explain her neurological symptoms were identified, and hemodialysis did not improve her mental state. Retrospective measurement of plasma and CSF ceftriaxone concentrations was performed by high-performance liquid chromatography using specimens collected at the onset of her consciousness disturbance (Fig. 2). The plasma and CSF concentrations of ceftriaxone were both found to be high (>100 μg/mL and 10.2 μg/mL, respectively), indicating that ceftriaxone neuro-

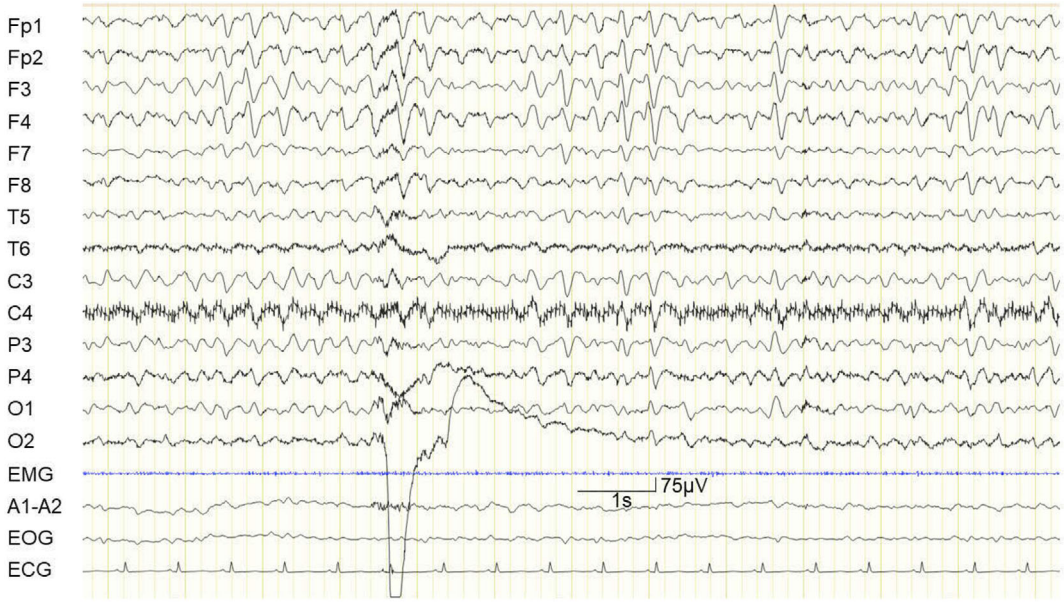

Figure 1. Electroencephalogram shows periodic generalized triphasic waves predominantly in the frontal area. EMG: electromyogram, EOG: electrooculogram, ECG: electrocardiogram

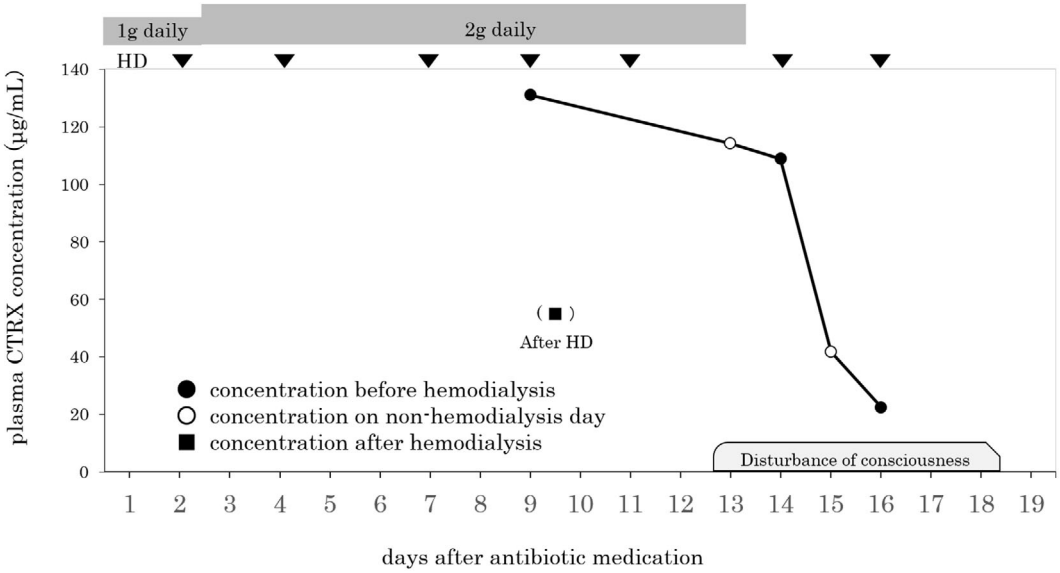

Figure 2. **The time course of the ceftriaxone concentration and administered dose. The concentrations were measured approximately 20 h after an infusion of ceftriaxone (2 g). The CTRX concentration rapidly decreased after discontinuation. CTRX: ceftriaxone, HD: hemodialysis**

toxicity was causally related to the adverse events in this case.

Discussion

Encephalopathy is known as an infrequent adverse effect of ceftriaxone (1-4). The exact mechanism that leads to ceftriaxone-induced encephalopathy as a side effect is not completely understood; however, it has been presumed to be caused by competitive antagonism of brain γ-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system (5), and increased excitatory amino acids (6).

The elimination half-life of ceftriaxone, which ranges from 6 to 9 hours in patients with a normal renal function, is longer than that of any other third-generation cephalosporin. Its elimination route is via kidney and biliary excretion; the half-life of ceftriaxone in hemodialysis patients was found to double from 8 to 16 hours in a previous study (7). Furthermore, unlike most cephalosporins that are highly dialyzable, ceftriaxone is not dialyzed during hemodialysis (8, 9). With renal failure, the accumulated toxic organic acids compete with cephalosporins for active transportation from the CSF to the blood, which increases the concentration of cephalosporin in the CSF (10).

In the present case, the patient presented with several risk factors for drug-induced neurotoxicity, including old age, renal impairment, and high-dose treatment (11). To clarify the association between ceftriaxone and encephalopathy, we measured the plasma and CSF concentrations of ceftriaxone. Although cefepime, a commonly used cephalosporin, is the only antibiotic mentioned in more than ten reports on the relationship between serum cephalosporin concentrations and neurotoxicity (12), no reports on ceftriaxone-induced encephalopathy have reported the drug concentrations associated with the condition. According to a previous report, after ceftriaxone (2 g, every 24 hours), the plasma trough levels ranged from 13 to 15 μg/mL in adults with a normal renal function (13). In the present case, the ceftriaxone plasma concentration before hemodialysis (approximately 20 hours after infusion of 2 g ceftriaxone) was >100 μg/mL. This value is far higher than that reported in a previous study (13), suggesting that a high plasma concentration of ceftriaxone was maintained ceftriaxone during administration. As already mentioned, the elimination half-life of ceftriaxone is longer in hemodialysis patients, which may lead to sustained high ceftriaxone concentrations in the plasma.

In the present case, the CSF ceftriaxone concentration was also high. Generally, the protein-unbound, free fraction of agents can freely penetrate the blood-brain/blood-CSF barrier (14). Approximately 90-95% of ceftriaxone is protein-bound and thus it can rarely penetrate the blood-CSF barrier (14). Nau et al. reported that the CSF concentrations of ceftriaxone after an infusion of ceftriaxone (2 g) in patients with uninflamed meninges ranged from 0.18 to 1.04 μg/mL (15), whereas the CSF ceftriaxone level in the current patient was 10.2 μg/mL even at more than 24 hours after the discontinuation of ceftriaxone. Furthermore, the free fraction of ceftriaxone is higher in patients with an abnormal renal function (4, 16). In the present case, the high proportion of unbound plasma ceftriaxone - due to the low albumin level and renal insufficiency - presumably made the CSF ceftriaxone concentration higher, resulting in neurotoxicity. The high proportion of unbound plasma ceftriaxone resulted in a relatively high rate of removal by dialysis; approximately 40% of ceftriaxone was dialyzed during hemodialysis.

Neurological manifestations of ceftriaxone-associated encephalopathy, such as myoclonus, asterixis, seizures, and consciousness alteration, have been reported in patients with an impaired renal function (3, 17). Previous studies reported that EEG findings such as slow waves and TWs might be associated with cephalosporin neurotoxicity. TWs are defined by their typical morphology, characterized by a predominant surface positive wave, preceded and followed by smaller surface negative deflections, conferring them a triphasic appearance (18). However, non-epileptic TWs with a sharply contoured morphology may resemble epileptic patterns encountered during nonconvulsive status epilepticus (NCSE), thus leading to the misinterpretation and over-interpretation of this pattern as ictal, if the electroencephalogram is considered alone (19). According to a previous study that described the electroencephalographic differences between TWs and NCSE, amplitude predominance of phase two was more common with TWs than with NCSE (40.8% vs. 0%); and the frequency of epileptiform discharge with TWs was lower than that with NCSE (1.8 Hz vs. 2.4 Hz) (20). An electroclinical response to benzodiazepines and the evaluation of consciousness impairment should be considered to distinguish between TWs and NCSE (19).

Neurological symptoms and EEG findings emerge at 1-10 days after the initiation of the cephalosporin treatment and resolve several days after discontinuation (1-3, 21-23). Thus, EEG might be beneficial in the diagnosis and management of ceftriaxone neurotoxicity. The neurotoxicity induced by cephalosporins is reported to be reversible (1-3, 21-23). In the present case, the discontinuation of ceftriaxone resulted in marked improvements in the clinical symptoms without any sequelae.

In conclusion, ceftriaxone might cause encephalopathy with manifestations such as myoclonus, an altered mental state, a decreased level of consciousness, and changes in EEG findings. Hemodialysis patients are particularly vulnerable to ceftriaxone-induced encephalopathy. This first reported case of high in plasma and CSF concentrations of ceftriaxone in a patient who developed neurological symptoms following ceftriaxone treatment suggests a causal relationship between the administration of ceftriaxone and the onset of encephalopathy. Patients with renal impairment who develop such symptoms during ceftriaxone treatment should be evaluated for potential ceftriaxone-induced encephalopathy, and drug discontinuation should be considered as the treatment of choice.

The authors state that they have no Conflict of Interest (COI).

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