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Ceftazidime-induced Non-Convulsive Status Epilepticus (NCSE) in a pediatric patient with Literature Review

Pediatrik Hastada Seftazidime Bağlı Nonkonvülsif Status Epileptikus (NKSE) Olgusu; Seftazidime Bağlı NKSE

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Abstract

Cephalosporins are a class of antibiotics routinely prescribed for a variety of pediatric infections. Among uncommon adverse effects, cephalosporins can be neurotoxic and epileptogenic, particularly in patients with reduced renal function. Neurotoxic effects are most frequently observed in adults with impaired renal function, and they have rarely been recorded in children. An 11-year-old boy with chronic renal failure experienced non-convulsive status epilepticus two days after initiating intravenous cefazolin and ceftazidime with a pre-diagnosis of peritonitis. The patient's mental condition reverted to baseline within hours after intravenous antibiotic treatment was discontinued and appropriate antiepileptic and anticonvulsive therapy was started. Providers should investigate cephalosporin-induced non-convulsive status epilepticus clinically and electrophysiologically in any child with renal impairment who demonstrates acute changes in mental status or decreased awareness after initiating intravenous cephalosporins.

Keywords: Cephalosporin, Non-Convulsive Status Epilepticus, Renal Failure.

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Öz

Sefalosporinler, çeşitli pediatrik enfeksiyonların tedavisinde rutin olarak reçete edilen bir antibiyotik sınıfıdır. Seyrek görülen yan etkiler arasında, sefalosporinlerin özellikle böbrek fonksiyonu azalmış hastalarda nörotoksik ve epileptojenik olabileceği belirtilmiştir. Nörotoksik etkiler, özellikle böbrek fonksiyonu bozulmuş yetişkinlerde daha sık gözlenirken, çocuklarda nadiren bildirilmiştir. Kronik böbrek yetmezliği tanısı ile takip edilen 11 yaşındaki erkek hastada peritonit ön tanısı ile intravenöz sefazolin ve seftazidim tedavisine başladıktan iki gün sonra non-konvülsif status epileptikus tablosu gelişmiştir. Hasta intravenöz antibiyotik tedavisinin kesilmesi ve uygun antikonvülsan tedavinin başlatılmasının ardından birkaç saat içinde mental durumu normale dönmüştür. İntravenöz sefalosporin başlanmasının ardından akut mental durum değişiklikleri gösteren her çocuk hastada klinik ve elektrofizyolojik olarak sefalosporin kaynaklı non-konvülsif status epileptikus akla gelmesi gereken ön tanılardan biridir.

Anahtar Kelimeler: Sefalosporin, Nonkonvulzif Status Epilepticus, Renal Yetmezlik.

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Introduction

Cephalosporins are one of the most chosen classes of antibiotics for various types of infections because of their broad antibacterial spectrum and pharmacokinetic and pharmaco-dynamic features. Cephalosporins are classified into four generations according to their antibacterial ability. Neurotoxicity of cephalosporins was reported for all generations (1). While cephalosporin-related neurotoxicity can happen even with proper dose and during dialysis, predisposing variables include pre-existing central nervous system impairment, renal impairment, and excessive dosing (2).

Cephalosporin-related neurotoxicity can manifest as myoclonus, dystonic movements, tremor, asterixis, coma, seizure, encephalopathy, and status epilepticus. Non-convulsive status epilepticus (NCSE) is a rare but well-known side effect of cephalosporins in people with renal insufficiency (3). This disorder can result in varied degrees of altered consciousness in the absence of obvious motor signs. NCSE is defined as seizures that continue without convulsions for more than ten minutes without complete interictal recovery (4). The examination of an electroencephalogram (EEG) is essential for diagnosis of this illness, and EEG can reveal continuous or intermittent electrographic discharges. Here, we present a pediatric patient followed with renal failure and continuous ambulatory peritoneal dialysis (CAPD) who developed NCSE while being treated with intravenous cefazolin and ceftazidime for pre-diagnosis of peritonitis.

Materials and Methods

Case Report

An 11-year-old boy was brought to the outpatient clinic with complaints of fever, vomiting, and abdominal pain. He was diagnosed with chronic renal failure caused by posterior urethral valve. Since the patient had been receiving peritoneal dialysis for the previous six years, the current symptoms indicated peritonitis. He was hospitalized and administered intravenous cefazolin and intraperitoneal ceftazidime. During the fourth day of treatment, clinicians observed he was intermittently confused. At follow-up, he displayed a steady deterioration in his mental state, as well as disorientation and difficulty cooperating, occasionally featuring facial myoclonic jerks. He could be aroused, responded to queries, and obeyed directions at the time of the initial neurological evaluation. There were no focal neurological abnormalities found during the neurologic evaluation. Brisk deep tendon reflex and bilateral clonus were noted. His Glasgow Coma score was E4M6V4. Brain MRI showed periventricular white matter ischemic alterations (periventricular leukomalacia) in T1 series. Diffusion and SWI series were normal. His EEG (Figure-1) revealed constant 3-Hz bi/triphasic sharp waves, leading to the diagnosis of NCSE. After administering midazolam (0.1 mg/kg intravenously) and diazepam (10 mg intravenously), electrophysiological findings improved. He was treated with sodium valproate, which was initiated with loading dose of 20 mg/kg, intravenously and continued with oral maintenance therapy. His EEG background initially improved, nevertheless, throughout the course of the following hour, the persistent, widespread acute and slow wave activity reappeared. Intravenous levetiracetam and oral clonazepam were added as maintenance therapy because of the patient's intermittent drowsy state and EEG findings. As no alternate etiology for NCSE could not be identified, cephalosporin-induced NCSE was considered. Ceftazidime and cefazolin were discontinued, About two days after stopping the cephalosporin, clinical symptoms and EEG results improved. He was later discharged with full recovery. In the subsequent three months of follow-up, antiepileptic drugs were successfully discontinued and EEG results were entirely clear (Figure 2).

Discussion

Here, we report a male with renal failure who had developed NCSE with the treatment of cephalosporins. As a differantial diagnosis, we excluded if he had metabolic encephalopathy, severe hypertension, infectious diseases, and electrolyte imbalances which are the causes of altered consciousness in patients suffering from renal failure (5). His biochemical tests did not show electrolyte imbalance and, the renal function values were not increased compared to his baseline values. The blood pressure was at the 50th percentile for his age. During the NCSE period, the patient had been treated with antibiotics for peritonitis and, there was no increase in infectious biomarkers and he had no fever which is the main sign of the infections. However, since neurological deterioration occurred following antibiotic treatment, the lumbar puncture was planned to

exclude central nervous system infection by evaluating cerebrospinal fluid. However, the family did not consent to the procedure. The patient's EEG findings were consistent with NCSE. Clinical improvement was observed following the and the initiating antiepileptics and anticonvulsants and, discontinuation of the cephalosporins. This is proof that NCSE is related to cephalosporin treatment.

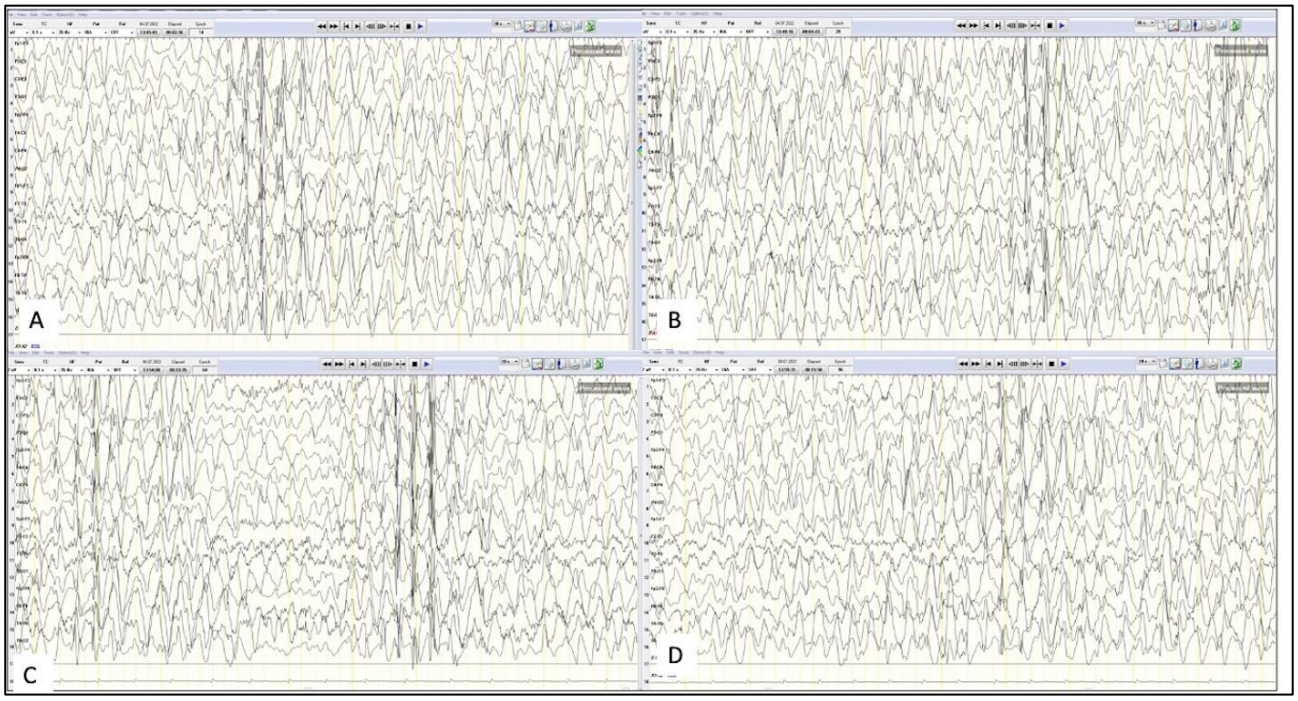

Figure 1. Preliminary electroencephalogram of the patient (during cephalosporin administration) suggestive of non-convulsive status epilepticus.
A)1st minute B) 5th minute C) 10 th minute D) 15 th minute

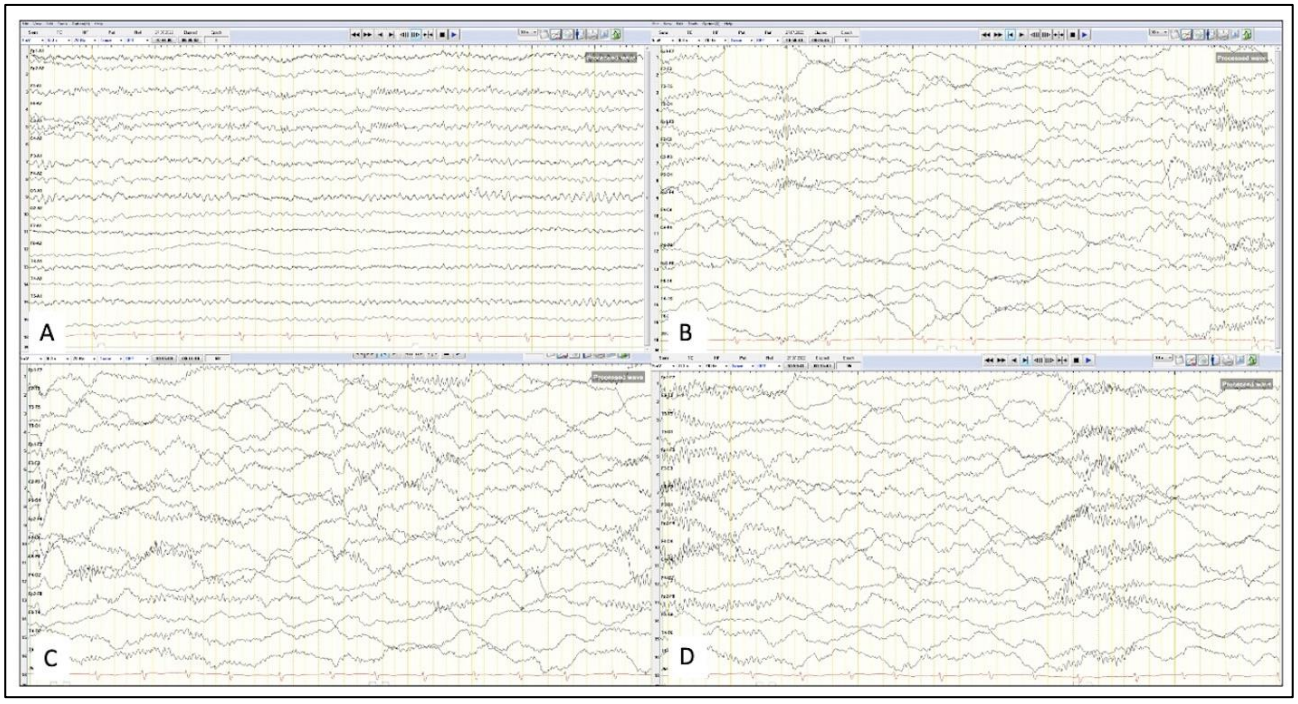

Figure 2. Control electroencephalogram – one week after discharge.
A)1st minute B) 5th minute C) 10 th minute D) 15 th minute

Neurotoxic adverse effects are caused by cephalosporins that can lead to status epilepticus, particularly NCSE, which is a well-known but unusual complication. Recent years have seen an increase in the number of reports

regarding the diagnosis of pediatric cephalosporin-induced NCSE. When a patient receives intravenous cephalosporin therapy and develops sudden changes in mental status, especially if they have any degree of renal failure, a diagnosis should be taken into consideration.It was reported that elderly patients are more likely to experience neurotoxicity since their creatinine clearance may decline with age. Here, we present a pediatric case with renal impairment diagnosed with NCSE, one of the neurotoxic effects of cephalosporins, while receiving intravenous cefazolin and intraperitoneal ceftazidime.

Cephalosporin-related neurotoxicity is thought to be associated with gamma aminobutyric acid (GABA)-A receptor antagonism because a part of the beta-lactam molecule resembles the chemical structure of the well-known GABA antagonist bicuculline (6,7). Inducing the release of endotoxins and TNF-alpha, which is associated with septic encephalopathy, and raising glutamate levels were considered as additional mechanisms contributing to neurotoxicity (8). Cefepime is the most frequently reported drug related to neurotoxicity among all generations of cephalosporins; however, ceftriaxone, ceftazidime, cefotaxime, and cefazolin were all cited (8). It is common practice in acute peritonitis to administer a combination of first and third-generation cephalosporins, cefazolin and ceftazidime, intraperitoneally on an intermittent or continuous basis (8). The size of the substituents at positions 7 (R1) and 3 (R2) in their 7-cephalosporanic acid structures determines the epileptogenesis of cephalosporin. Positions 7 and 3 on a cefazolin heterocyclic ring may increase the possibility of epileptogenesis.

Prior central nervous system (CNS) disorders, high dosage consumption, and renal insufficiency are risk factors for cephalosporin-induced neurotoxicity (3). Patients suffering from renal insufficiency are more susceptible to neurotoxic effects because of changed pharmacokinetics that lead to raised blood urea nitrogen and cephalosporin concentrations in circulation. Additionally, the permeability of the blood-brain barrier is increased by glycated and carbamylated proteins (10). However, active peritonitis may raise membrane permeability and hence raise antibiotic absorption, raising the possibility of systemic toxicity (9). From the peritoneal cavity, ceftazidime is absorbed and enters the bloodstream. Compared to individuals who are not infected, patients with peritonitis absorb more medication from the peritoneal cavity (3). Despite being administered at authorized dosages, patients with renal impairment are more susceptible to ceftazidime neurotoxicity because the medication is not digested by the body and is eliminated unchanged in the active form in the urine by glomerular filtration (11). As a result of renal failure and peritonitis, our patient was in the risk group for cephalosporin neurotoxicity.

The onset of neurotoxicity can occur one to ten days later. After stopping cephalosporin medication, documented neurological problems frequently subside in two to seven days (1,12). The clinical condition of our patient worsened on the fourth day of cephalosporin medication. Symptoms began to improve two days after cephalosporin discontinuation.

Although NCSE was reported in patients with renal disease, neurotoxicity was also reported in cases without renal function problems (13). The diagnosis of drug-induced NCSE has become more common in recent years, and patients who experience sudden changes in their mental state while receiving intravenous cephalosporin treatment—especially those with some degree of renal dysfunction—should have this condition evaluated. An urgent EEG should be taken into account. The use of electroencephalography is necessary for precise diagnosis (4). Working criteria for the EEG diagnosis of NCSE were proposed by a consensus panel at the 4th London-Innsbruck Colloquium on status epilepticus and acute seizures, which was held in Salzburg in 2013 (Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus, SCNC). Our patient was diagnosed with NCSE with continuous 3 Hz generalized spike and wave activity based on these criteria.

Myoclonic seizures, aberrant conduct, mutism, ataxia, asterixis, hallucinations, tremor, clonus, and hyperreflexia are among the clinical signs other than altered awareness that have been documented (6). Case reports have shown brief myoclonic seizures prior to NCSE, as was the situation with our patient (10).

Our case is an example of NCSE due to the neurotoxicity of cephalosporin at a therapeutic dosage in a pediatric patient with renal failure. It is important that this event should be considered in pediatric patients, although the majority of cases were reported at older ages. A summary of the previously reported pediatric patients with cephalosporin-induced NCSE is shown in Table 1. Most of the pediatric cases reported in the literature were related to cefepime. However, our case is significant due to its association with ceftazidime.

Tablo 1.

The Summary of Patients with The Diagnosis of Cephalosporin-Induced Non-Convulsive Status Epilepticus

References	Age of patient/ sex	Comorbidities	Drug	NCSE symptoms	Cranial imaging	EEG findings	Treatment	Follow up
Chedrawi et al., 2004 (13)	12-years/ Female	Chronic renal insufficiency secondary to congenital renal dysplasia.	ceftriaxone for possible sepsis	progressively more confused and unresponsive occasional myoclonic twitches of the face	CT: normal	Bursts and runs of generalized spike and spike wave discharges *are recorded over a period of 90 seconds.* Generalized triphasic and slow waves	diazepam , phenytoin,, benzodiazepine Ceftriaxone was discontinued	the following day, mental status dramatically improved , became awake, coherent and able to follow verbal commands. complete resolution of the epileptiform discharges within 24 hours after discontinuing ceftriaxone background remained slow, likely a postictal effect.
Alpay et al., 2004 (14)	15years/Male	End-stage renal disease secondary to focal segmental glomerulosclerosis	intravenous cefepime for pneumonia	gait abnormality, difficulty in writing and reading, memory problems. progressive confusion	CT: did not show any acute abnormalities. MRI : normal	consistent with status epilepticus	diazepam phenytoin Cefepime therapy was discontinued	No neurological findings and with normal EEG (after 1 year follow-up)
Thabet et al., 2009 (15)	15-years / Female	End stage renal disease secondary to polycystic kidney on hemodialysis	IV cefepime for blood culture showed Pseudomonas aeruginosa	Lethargic and confused. (Glasgow coma scale of 8), myoclonic jerks	CT scan brain were unrevealing	Generalized spike and sharp wave activity compatible with NCSE	Midazolam con-tinuous infusion. İntubation Cefepime was discontinued	the patient regained full consciousness (Glasgow coma scale of 15) after 48 hours repeated EEG was normal

Nichols et al., 2011 (16)	A 15-year-old,	Cystic fibrosis Acute kidney injury	IV cefepime for lower respiratory cultures contained MSSA and *Stenotrophomonas maltophilia*, with past cultures significant for *P. aeruginosa*.	Sleepy poorly responsive.	Not available	An electroencephalogram (EEG) was not obtained due to extubation of the patient	Hemodialysis	At a 2-week follow-up clinic visit, the patient was recovering well,
Landgrave et al., 2012 (17)	14 years / Female	McCune-Albright syndrome, hypoparathyroidism, hypothyroidism, asthma, hypogammaglobulinemia, factor V Leiden deficiency, deep vein thrombosis, worsening kidney failure during antibiotic treatment.	intravenous cefepime and meropenem for septic hip artiritis	deteriorated right-sided face twitching sleeping, sedated	CT: mildly prominent lateral ventricles, with otherwise normal findings.	Requent, irregular, generalized polyspike wave discharges High-amplitude nonrhythmic slowing, and 2-second periods of background suppression or attenuation. After pentobarbital infusion :burst suppression	midazolam drip levetiracetam. pentobarbital infusion Cefepime was discontinued Meropeme was discontinued	
Ekici et al., 2012 (18)	Case1(C1) : 15 years / Female Case2 (C2) : 7 years / Female	C1: Chronic renal failure who was on continuous ambulatory peritoneal dialysis (CAPD) C2: Hypertension and chronic renal failure secondary to bilateral vesico-ureteral reflux	C1: Intraperitoneal and intravenous (IV) ceftazidime and vancomycin for peritonitis C2: IV cefepime for open bilateral ureteroneocystostomy	C1: Headache, drowsiness, myoclonic jerks and ataxia. C2: confused demonstrated inappropriate crying, agitation involuntary movements of the head and hands.	C1: (MRI) was normal. C2:not available	C1: diffuse slow-spike waves and triphasic waves C2: diffuse slow-spike waves	C1: ceftazidime was discontinued oral valproate C2: cefepime was discontinued, iv diazepam , oral sodium valproate	C1: Began to communicate after 24 hours. Myoclonus disappeared (on the fifth day of treatment) the EEG normalized after 6 days. C2: symptoms were disappeared after 2days EEG findings were normalized after 10 days.

Shah et al. , 2021(19)	13years/ Female	major depressive and behavioral disorder, focal segmental glomerulosclerosis, subsequent hemodialysis dependent end-stage renal diseas	intravenous cefepime for cathether infection	difficulty in walking and grasping items. aphasia visual hallucinations	CT: did not show any acute abnormalities. MRI :unremarkable	mild background slowing, multifocal and diffuse epileptiform discharges, generalized excessive beta intermittently, slowing in the right posterior quadrant, left posterior quadrant, and central head regions	lorazepam levetiracetam phenobarbital Cefepime therapy was discontinued hemodialysis	back to her neurologic baseline with normal GCS within 24 hours
Nguyen et al. 2022 (12)	16 years/ Female	Chromosome 10-15 unbalanced translocation, spastic quadriplegic cerebral palsy, epilepsy, hydrocephalus with VP shunt, tethered cord syn-drome Tracheostomy fundoplication, scoliosis, and thoracic lordosis status post spinal fusion, and global developmental delay.	intravenous cefepime, linezolid and vancomycin for positive Escherichia coli urine cultures, positive Pseudomonas spp. respiratory cultures, Clostridium difficile prophylaxis	less responsive than usual Intermittent extensor posturing was noted with tactile stimuli, no other response to noxious stimuli.	CT head : showed expected pneumocephalus with mild soft tissue swelling over the left frontal scalp	Rhythmic 2.5-3 Hz generalized epileptiform discharges	levetiracetam, lorazepam, phenobarbital Cefepime was discontinued	Back to her baseline state of health within 2 days after discontinuing cefepime
Hambrick et al., 2022 (20)	2 years /	Chronic kidney diseas	IV cefepime for *Serratia marcescens* bacteremia	Agitation, tremor, and inconsolability	No data avaliable (abstract only)	No data avaliable (abstract only)	Cefepime was discontinuation	No data avaliable (abstract only)

In conclusion; while there are no defined standard criteria for the therapy of this condition have not been established, discontinuation of antibiotics, administration of antiepileptic drugs, and receiving supportive treatment are suitable measures to take. In this potentially curable illness, prompt detection and diagnosis are critical because protracted diagnostic delays may raise morbidity or death. Clinicians and doctors should be more aware of the possible neurotoxicity of ceftazidime and other cephalosporins because their usage is growing more widespread.

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References

1. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother. 2008;42(12):1843-50.
2. Kim KB, Kim SM, Park W, Kim JS, Kwon SK, Kim HY. Ceftriaxone-induced neurotoxicity: case report, pharmacokinetic consideration, and literature review. J Korean Med Sci 2012; 27(9): 1120–3.
3. Bora I, Demir, AB, Uzun, P. Nonconvulsive status epilepticus cases arising in connection with cephalosporins. Epilepsy Behav Case Rep. 2016; 6: 23-7.
4. Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol. 2021; 38(1): 1-29.
5. Primavera A, Cocito L, Audenino D. Nonconvulsive status epilepticus during cephalosporin therapy. Neuropsychobiology. 2004;49(4):218-22.
6. Vannaprasaht S, Tawalee A, Mayurasakorn N, Yodwut C, Bansong R, Reungjui S et al. Ceftazidime overdose-related nonconvulsive status epilepticus after intraperitoneal instillation. Clin Toxicol (Phila). 2006; 44(4): 383-6.
7. Wallace KL. Antibiotic-induced convulsion. Crit Care Clin 1997; 13(4): 741–62.
8. Sugimoto M, Uchida I, Mashimo T, Yamazaki S, Hatano K, Ikeda F. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. Neuropharmacology. 2003; 45(3): 304–14.
9. Chen CC, Lee DJ, Lin SH. Reversible cefazolin-induced status epilepticus in a peritoneal dialysis patient. Toxicol Rep. 2022; 9: 1950-2.
10. Al-Sadawi M, Rodriguez Ortega R, Sun N, Abdurahimova M, McFarlane SI. Jerky Movement with Ceftazidime: A Case of Ceftazidime-Induced Neurotoxicity with a Review of the Literature. Case Rep Med. 2019;2019:8936478.
11. Ong CY, Qin Y. Myoclonus from Antibiotic Therapy (Ceftazidime-induced Neurotoxicity): A Case Report and Review. Cureus. 2018; 10(3): e2250.
12. Roncan-Albuquerque R, Pires I, Martins R, Real R, Sousa G, Von Hafe P. Ceftriaxone-induced acute reversible encephalopathy in a patient treated for a urinary tract infection. Neth J Med. 2009; 67(2): 72-5.
13. Nguyen C, Clegg T, Kumar A, Paudel S. Cefepime-Induced Nonconvulsive Status Epilepticus in a Pediatric Patient with Normal Renal Function. Child Neurol Open. 2022; 9:2329048X221119575.
14. Chedrawi AK, Gharaybeh SI, Al-Ghwery SA, Al-Mohaimeed SA, Alshahwan SA. Cephalosporin-induced nonconvulsive status epilepticus in a uremic child. Pediatr Neurol. 2004;30(2):135-9.

15. Alpay H, Altun O, Biyikli NK. Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. Pediatr Nephrol. 2004;19(4):445-7.
16. Thabet F, Al Maghrabi M, Al Barraq A, Tabarki B. Cefepime-induced nonconvulsive status epilepticus: case report and review. Neurocrit Care. 2009;10(3):347-51.
17. Nichols KR, Brown DM, Knoderer CA, Andreoli SP. Cefepime Neurotoxicity in an Adolescent Cystic Fibrosis Patient with Aminoglycoside-Induced Acute Kidney Injury. Journal of Pharmacy Technology. 2011;27(4):164-7.
18. Landgrave LC, Lock JL, Whitmore JM, Belcher CE. Pediatric cefepime neurotoxicity. Pediatr Neurol. 2012;47(6):458-60.
19. Ekici A, Yakut A, Kural N, Bör Ö, Yimenicioğlu S, Çarman KB. Nonconvulsive status epilepticus due to drug induced neurotoxicity in chronically ill children. Brain Dev. 2012;34(10):824-8.
20. Shah S, Bland S. Cefepime-Induced Encephalopathy With Seizures in a Pediatric Patient With End-Stage Renal Disease Rapidly Reversed by High-Efficiency Hemodialysis. Cureus. 2021;13(3):e13842.
21. Hambrick HR, Pavia K, Tang Girdwood S, Lazear D, Taylor JM, Benoit S. Cefepime-Associated Neurotoxicity in a Pediatric Patient With Stage V Chronic Kidney Disease. J Pharm Pract. 2024;37(1):243-7.