Ceftazidime-induced neurotoxicity in a peritoneal dialysis patient

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SUMMARY

Cephalosporins are commonly used broad-spectrum antibiotics in clinical practice. However, neurotoxicity is an underrecognized side effect of this antibiotic group, especially cefepime and ceftriaxone, owing to their special pharmacokinetic profile. It can manifest as encephalopathy, seizures and myoclonus, which may share a similar presentation as other acute pathology. The risk of neurotoxicity is higher among elderly and renal failure patients. This case involved a lady in her 60's with end-stage kidney disease on automated peritoneal dialysis and major depressive disorder, who developed acute psychosis and myoclonic seizures during the treatment for peritoneal catheter exit site infection using high-dose ceftazidime. Symptoms resolved after discontinuation of ceftazidime and use of antipsychotics and antiepileptics. Patient was discharged well, with normal neurology and mental status. This case illustrated the difficulty of distinguishing treatment-induced neurotoxicity from other concomitant acute medical illnesses and the possible deterioration of preexisting psychiatric illness. Thus, clinicians must be aware of appropriate antibiotic dosage and able to identify the predisposing factors of neurotoxicity. Although cephalosporin-induced neurotoxicity is mostly self-limiting following discontinuation of the antibiotic, severe cases may need additional supportive measures.

INTRODUCTION

Cephalosporins are among the commonest prescribed antibiotics in clinical practice owing to the broad spectrum of coverage. Hypersensitivity reactions are most commonly reported with the use of cephalosporins, ranging from mild cutaneous reactions to severe anaphylaxis, followed by acute interstitial nephritits and *Clostridium difficile* infection.[1] In fact, cephalosporins can also potentially cause encephalopathy, seizure and myoclonus due to their pharmacokinetic properties. Literature reported that neurological adverse effects are most evident with cefepime, followed by ceftriaxone, ceftazidime, cefotaxime, and cefazolin, in descending order.[2] A study reported a prevalence rate of 15% for cefepime-induced neuropathy among critically ill patients in the intensive care unit (ICU).[3] However, the true prevalence rate of cephalosporin-induced neurotoxicity was masked by underrecognition of the problem due to concomitant medical illness and underreporting due to a lack of objective laboratory diagnosis.

Here, we present a case of a 64-year-lady with psychiatric illness and end-stage kidney disease (ESKD) on automated peritoneal dialysis (APD) who developed encephalopathy and myoclonic seizures while being treated with high dose ceftazidime for *Pseudomonas aeruginosa* catheter site infection.

CASE PRESENTATION

This is a 64-year-old Malay woman, with a background history of diabetes mellitus type II, hypertension, dyslipidemia, ischaemic heart disease and anuric ESKD on APD. She also had major depressive disorder (MDD), which was stable on medications under psychiatric follow-up. She was recently admitted to nephrology ward in another hospital, being treated for local peritoneal dialysis catheter exit site infection. Swab culture yielded *Pseudomonas aeruginosa*. She was planned for outpatient treatment of oral Ciprofloxacin 250 mg twice daily and intravenous (IV) Ceftazidime 2 g on alternate days. On day 6 of treatment, after the third dose of IV Ceftazidime, she became aggressive and started to have auditory and visual hallucinations. Family members also noticed paroxysmal abnormal jerking movements of her limbs. She did not have a fever or abdominal pain since being discharged from the nephrology unit. APD was uneventful at home. She was brought to our hospital on day 8 of outpatient treatment. The last IV ceftazidime was administered on the day of admission before being admitted. Her body weight was estimated to be 60 kg. On presentation, she was afebrile. Her blood pressure and heart rate were 155/84 mmHg and 103 beats per minute, respectively. She was not tachypneic and saturated well on room air. She was disorientated, and Glasgow Coma Scale was 10 (GCS E4V1M5). Cardiovascular and respiratory system examinations were normal. Neurological examination of the limbs and cranial nerves were unremarkable, and there was no abnormal movement noted. There was no sign of acute peritonitis. Exit site was clean and dry.

Full blood count showed a normal total white cell count 8.0 x 10^3/µL, neutrophils 4.69 x 10^3/µL. The urea was 11.6 mmol/L, sodium was 146 mmol/L, potassium was 4.1 mmol/L, and creatinine was 975µmol/L. Serum albumin was 28 g/L, and her liver enzymes were normal. Corrected serum calcium was 2.20mmol/L. Magnesium level was 0.9 mmol/L, and phosphate level was 2.26 mmol/L. C-reactive protein was 7.15 mg/L, which was mildly raised. Blood glucose ranged

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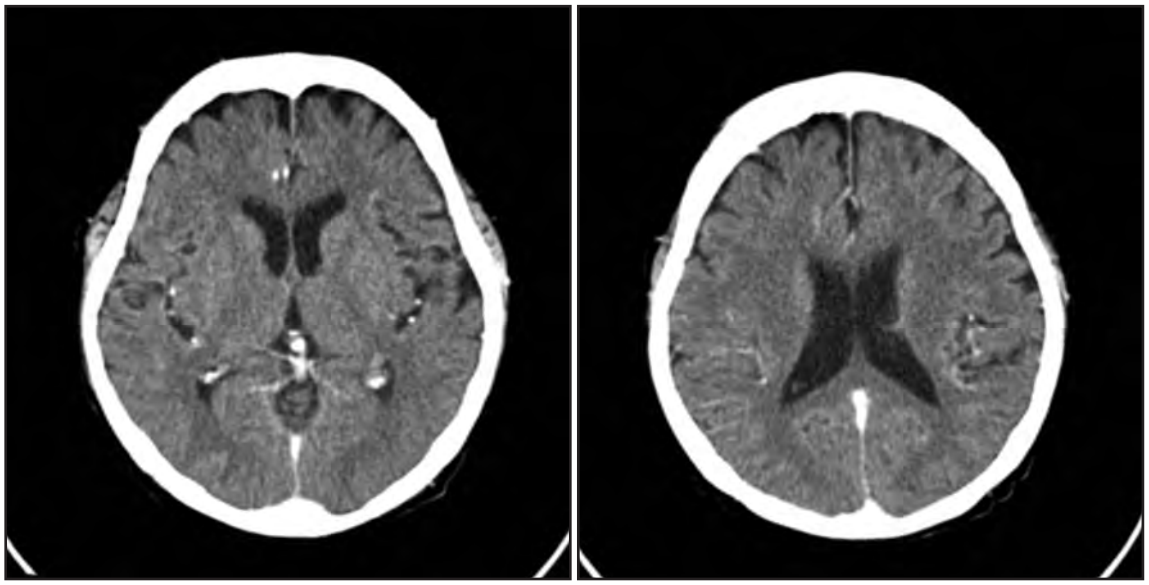

Fig. 1: Contrast-enhanced computed tomography of the patient's brain on day 1 of admission

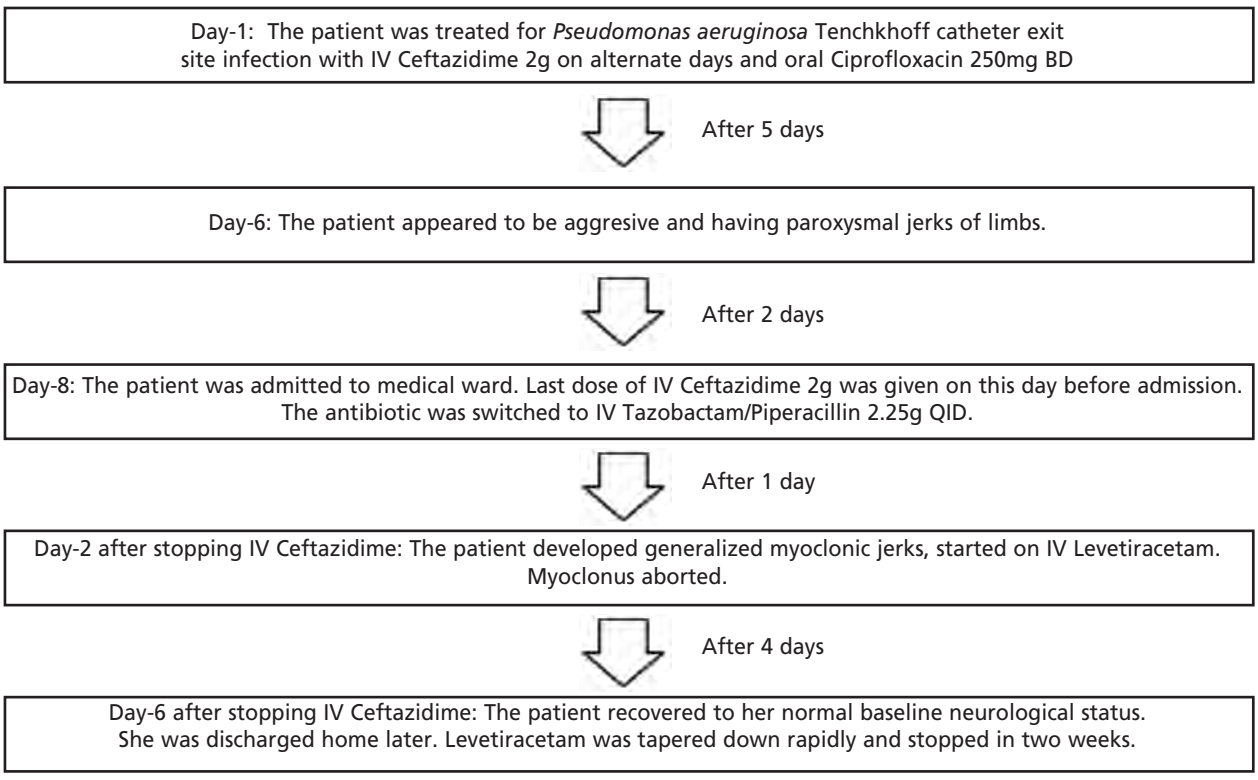

Fig. 2: Timeline of the patient's presentation

from 6.8-9.9mmol/L. Chest X-ray was unremarkable. Contrast-enhanced computed tomography (CT) of the brain showed only age-related cerebral atrophy, without any significant abnormality (Figure 1). Lumbar puncture was done. Cerebrospinal fluid (CSF) analysis showed only mildly elevated protein 0.67 g/L, but the other parameters are not suggestive of acute infection. Blood and CSF cultures were negative.

In ward, IV ceftazidime was changed to IV piperacillin/tazobactam for empirical treatment of sepsis. Oral ciprofloxacin was continued. Oral fluconazole was given as fungal prophylaxis. Gentamicin cream 0.1% was given as topical antibiotic. She was intermittently aggressive and had incoherent speech. Haloperidol was started to control her positive behaviours. On second day of admission, she developed myoclonic jerks of all limbs and face in ward and was treated with intravenous levetiracetam. Repeated CT imaging of the brain was unremarkable. Blood culture and CSF culture showed no bacterial growth. Subsequently, the patient still appeared lethargic but gradually improved to her baseline mental state on day 6 of admission. Electroencephalogram (EEG) was not done in time due to the complete neurological recovery. Intravenous antibiotics were continued for another 2 weeks for the treatment of exit site infection. Levetiracetam dose was tapered down and discontinued over 2 weeks. She was discharged well without any neurological deficit (Figure 2).

DISCUSSION

The mechanism of cephalosporins-induced neurotoxicity involves the inhibition of gamma-aminobutyric acid (GABA) binding to its receptors, leading to the hyperexcitability of neurons. Other mechanisms, like induction of endotoxins and facilitation of excitatory neurons, especially N-methyl-D-aspartate (NMDA) receptors, were also proposed.[4] Ceftazidime is not metabolised in the body, and up to 90 percent is excreted unchanged in the urine via the kidneys by glomerular filtration.[5] Therefore, neurotoxicity is common in elderly and renal impairment due to a longer half-life of the drug. Patients with underlying cerebral disease are at an even higher risk of developing neurotoxicity.[6] Clinical presentations of ceftazidime-induced neurotoxicity are heterogenous. A review of 12 cases of ceftazidime-induced neurotoxicity in patients with a mean age of 65 years and variable degree of renal insufficiency by Chow et al showed that the most frequent symptoms were confusion, myoclonus and generalised seizure, with incidence rates of 91%, 50% and 8%, respectively.[7] This case report highlighted the fact that this patient had an acute infection, ESKD and underlying psychiatric illness made the diagnosis of cephalosporin-induced neurotoxicity difficult as there were many other more common differential diagnoses, including uremia, electrolyte imbalance, major depressive disorder with psychosis, acute meningoencephalitis and septic encephalopathy. However, the blood and imaging results were not indicative of any of these factors. In this case, the diagnosis of ceftazidime neurotoxicity was made by exclusion of other common causes, and based on the temporal association of the development of encephalopathy and myoclonus after starting ceftazidime, and the resolution following discontinuation of cephalosporins. EEG is also useful to support the diagnosis in this case, though the findings are not specific.[6,7]

In peritoneal dialysis patients with exit site infection, intraperitoneal (IP) route of antibiotic would be a preferable choice.[8] Combination of ciprofloxacin and ceftazidime is given in patients with slow-resolving or recurrent Pseudomonas aeruginosa exit-site infection.[8] Intermittent dosing of IP ceftazidime (1000–1500 mg/day) may be given as day-dwell in patients on APD.[9] Alternate day dosing of IV ceftazidime of 2 g in this patient may lead to high peak dose on administration, which might have predisposed her to higher risk of neurotoxicity, in addition of age factor, evidence of old cerebral infarct and ESKD. A pharmacokinetic study suggested intravenous administration of 15 mg/kg ceftazidime in APD patients every 24 hours can be used to treat systemic or intraperitoneal infections, but data on the pharmacokinetic profile after repeated administration still lacks.[10] It is not common to monitor blood cephalosporin levels, thus careful monitoring for clinical manifestations of cephalosporin-induced neurotoxicity among these vulnerable groups of patients is very important. The typical time of onset of neurotoxicity ranges from two to ten days of initiation of the cephalosporin. It resolves 2–7 days following discontinuation. Discontinuation of cephalosporins and supportive care are usually sufficient.[6,7] Intermittent hemodialysis was described as a treatment for cephalosporin-induced neurotoxicity, owing to the dialyzability of cephalosporin.

CONCLUSION

Clinicians must be aware and able to identify high-risk patients and recognise the clinical manifestations of cephalosporin-induced neurotoxicity. The dosage of antibiotics has to be adjusted according to individual renal functions, body weight and clinical indications. Supportive care and withdrawal of cephalosporins are the mainstay of the treatments, but specific measures i.e. antiepileptics, antipsychotics or sedations are sometimes needed depending on the disease severity.

ETHICAL ISSUES

Written consent to publish this case report was taken from the patient. This case report has obtained approval from the National Medical Research Register (NMRR), Ministry of Health Malaysia: NMRR-21-1429-60929

DECLARATIONS OF INTEREST

None

DISCLOSURE

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REFERENCES

1. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. J Allergy Clin Immunol 2015; 135(3): 745-52.
2. Lacroix C, Kheloufi F, Montastruc F, Bennis Y, Pizzoglio V, Micallef J. Serious central nervous system side effects of cephalosporins: a national analysis of serious reports registered in the French Pharmacovigilance Database. J Neurol Sci 2019; 398: 196-201.
3. Fugate JE, Kalimullah EA, Hocker SE, Clark SL, Wijdicks EF, Rabinstein AA. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. Critical Care 2013; 17(6): 1-6.
4. Sugimoto M, Uchida I, Mashimo T, Yamazaki S, Hatano K, Ikeda F, et al. Evidence for the involvement of GABA receptor blockade in convulsions induced by cephalosporins. Neuropharmacology 2003; 45(3): 304-14.
5. Lutsar I, Friedland IR. Pharmacokinetics and pharmacodynamics of cephalosporins in cerebrospinal fluid. Clin Pharmacokinetics 2000; 39(5): 335-43.
6. 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.
7. Chow KM, Szeto CC, Hui AC, Wong TY, Li PK. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. Pharmacotherapy 2003; 23(3): 369-73.
8. Szeto CC, Li PK, Johnson DW, Bernardini J, Dong J, Figueiredo AE, Ito Y, et al. ISPD catheter-related infection recommendations: 2017 update. Peritoneal Dial Int 2017; 37(2): 141-54.
9. Li PK, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. Peritoneal Dial Int 2022; 42(2): 110-53.
10. Kim K, Hwang YH, Ro H, Oh YK, Kim MG, Yu KS, et al. Pharmacokinetic profiles of ceftazidime after intravenous administration in patients undergoing automated peritoneal dialysis. Antimicrobial agents Chemother. 2011; 55(6): 2523-7.