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Case Report

Ceftriaxone-Induced Non-Convulsive Status Epilepticus in an Elderly Patient with Renal Insufficiency

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SUMMARY

Ceftriaxone, third-generation cephalosporin, is widely used in patients for the treatment of serious gram-negative infection without a dose adjustment for renal insufficiency. Ceftriaxone–induced neurotoxicity, particularly non-convulsive status epilepticus (NCSE), has rarely been reported. We present a case of ceftriaxone–induced non-convulsive status epilepticus in treatment of complicated urinary tract infection and acute on chronic kidney disease (CKD) for a 71-year-old woman. The prognosis of NCSE is poor in elderly patients due to a delay in diagnosis and treatment may be associated with increased mortality or neuronal loss, as well as dysfunction of cognitive and behavioral abilities. Emergent and continuous electroencephalogram monitoring can assist physicians in both early recognition and accurate management of NCSE. Immediate withdrawal of cephalosporin is necessary. Antiepileptic drugs may be helpful but data of prognosis are still lacking. Physicians should be aware of the potential neurotoxic complication in those with high risks (elderly, CKD, or prior central nervous system conditions).

1. Introduction

Cephalosporins are broad spectrum and most frequently used β-lactam antibiotics for treatment of serious gram-negative infection due to excellent tissue penetration. Ceftriaxone is a third-generation cephalosporin, long half-life, easy through blood-brain-barrier and penetration into cerebrospinal fluid. Compared with other cephalosporins, a dose adjustment for renal insufficiency is not required for ceftriaxone, which makes it more convenient for patients in advanced age or chronic kidney disease (CKD). While using β-lactam antibiotics, toxicity in the central nervous system (CNS) is rare but had been reported several times in treatment of intravenous cephalosporins (particularly, cefepime, fourth-generation), penicillins and carbapenems.[1,2] Neurotoxic side effects may manifest in a variety of clinical presentations, including myoclonus, dystonic movements, tremor, asterixis, seizure, status epilepticus, encephalopathy, and even coma.[1] Patients who are elderly, those with renal insufficiency, those with prior central neurological disease may be particularly prone to these neurotoxic side effects.[1,3] Non-convulsive status epilepticus (NCSE) is a condition of status epilepticus with different levels of altered mental status without obvious motor signs. It is clinically crucial that NCSE needs to be detected by electroencephalogram (EEG) with a variety of manifestations, continuous or intermittent epileptic discharges. The prognosis of NCSE is poor, because a delay in diagnosis and treatment may be associated with increased mortality or neuronal loss, as well as dysfunction of cognitive and behavioral abilities, especially in elderly patients.[4,5] Compared with other β-lactam antibiotics, ceftriaxone-induced NCSE is rarely reported.[2] We present a case of 71-year-old woman who developed NCSE after 5 day use of ceftriaxone during recovering from acute on chronic kidney disease.

2. Case report

A 71-year-old woman, consciousness clear, no pre-existing central nervous system (CNS) conditions had type 2 diabetes mellitus (T2D) with chronic kidney disease (CKD) stage 5, neurogenic bladder with indwelling Foley catheter. She had been hospitalized for several times due to complicated urinary tract infection (UTI) in past few years. This time, on May 10, 2016, she was admitted to our hospital due to recurrence of complicated UTI and acute kidney injury. She presented with turbid urine, poor appetite, intermittent nausea and vomiting before hospitalization. Her initial laboratory data upon admission were as following: WBC 12.8^10^3/μL (3.8–10.0), C.R.P. 2.2 mg/dL (≤1.0), S-GPT 9IU/L (6–45), Na 127.5 mmol/L (136–144), K 5.5 mmol/L (3.6–5.1), Glucose 106 mg/dL (80–110), Albumin 3.4 g/dL (3.8–5.3) Bun 104 mg/dL (8–20), Serum creatinine 8.17 mg/dL (0.44–1.03) (4 weeks before admission: 5.97 mg/dL), which demonstrated the progressively deteriorated renal function. Arterial blood gas showed mixed respiratory alkalosis/metabolic acidosis (PH 7.39 (7.35–7.45), PCO_2 29.3 mmHg (35–46), PO_2 108.8 mmHg (80–100), HCO_3 17.6 mmol/L (22–26), CO_2 18.5 mmol/L (24–28), BE -5.8 mmol/L (2), SaO_2 98.0% (95–100) in room air). Her kidney echo was compatible with acute on chronic pyelonephritis on bilateral kidneys. Ceftriaxone (2g/day) was chosen to administer intravenously

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for empiric treatment of UTI, which was based on her prior urine bacteria cultures during previous hospitalization with resistance to first/second-generation cephalosporin and quinolone. Her renal function and infection were improving in the day 5 check-up (WBC 8.4^10^3/μL, Na 139 mmol/L, K 3.8 mmol/L, Bun 44 mg/dL, Serum creatinine 5.23 mg/dL). On day 6 of hospitalization, her consciousness suddenly changed into stupor (Glasgow coma scale: E2M1V1) without any myoclonic jerks. Her muscle power of four limbs was 0. Both pupil sizes were 3 mm and light reflexes were intact. Normal brainstem reflexes (oculovestibular and oculocephalic reflexes), as well as Babinski's sign, were noted. A brain computed tomography (Fig. 1.) without contrast as well as the laboratory data demonstrated no abnormality to explain her neurologic findings. An emergent EEG on the same day showed continuous, generalized periodic epileptiform discharges, ranging from 0.5 to 3 Hz without visible background rhythm (Fig. 2.). Ceftriaxone–induced NCSE was highly suspected (except for ceftriaxone, she was only used mitiglinide 10 mg thrice daily and insulin detemir 12 units once daily for T2D).

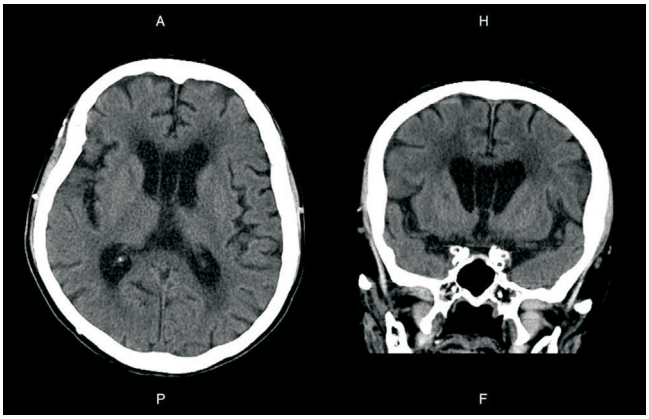

Fig. 1. Brain CT revealed no evidence of intracranial bleeding, an organic brain lesion or acute infarction.

Ceftriaxone was subsequently discontinued. However, the patient's consciousness was still not improved. One day later (day 7), the intravenous antiepileptic drug, valproic acid (400mg Q8H) was started to administer. Her vital signs were smoothly in the following days but her consciousness was still E1-2M1V1. On day 10 of hospitalization, she presented sudden onset of apnea and asystole. Cardiopulmonary resuscitation for 30 minutes was done but failed. The patient died with no evidence of hyperkalemia, acidosis or hypovolemia, but may be related to poor outcome of NCSE.

3. Discussion

Infection and chronic kidney disease (CKD) are very common clinical problems in elderly patients.[6,7] Both CKD and older age are known to be important risk factors in cephalosporin-induced neurotoxicity.[1,2] Ceftriaxone is thought to be one of low risk agents associated with neurotoxicity in cephalosporins and clinically convenient to use in patients of advanced age or CKD due to no dosage adjustment for renal insufficiency.[2,8] In this case report, we described a case of NCSE following the administration of ceftriaxone to treat complicated UTI in an elderly patient with severe renal function impairment. It is difficult to choose a proper antimicrobial agent because of her previous urine bacteria cultures, of which high resistance to first/second-generation cephalosporin and quinolone. Moreover, neurotoxicity are more often reported to be associated with both fourth-generation cephalosporin (especially, cefepime) and carbapenems.[1,9–14] Therefore, ceftriaxone seemed inevitably to be the last straw that broke the camel's back at this patient to induce neurotoxicity.

Neurotoxicity from cephalosporins may vary from myoclonus, seizure to NCSE and coma. Latency in development of neurotoxicity varied from one to ten days following start of the medication, and resolution in two to seven days following discontinuation.[15] The basic mechanism for neurotoxicity has been proposed to be mediated

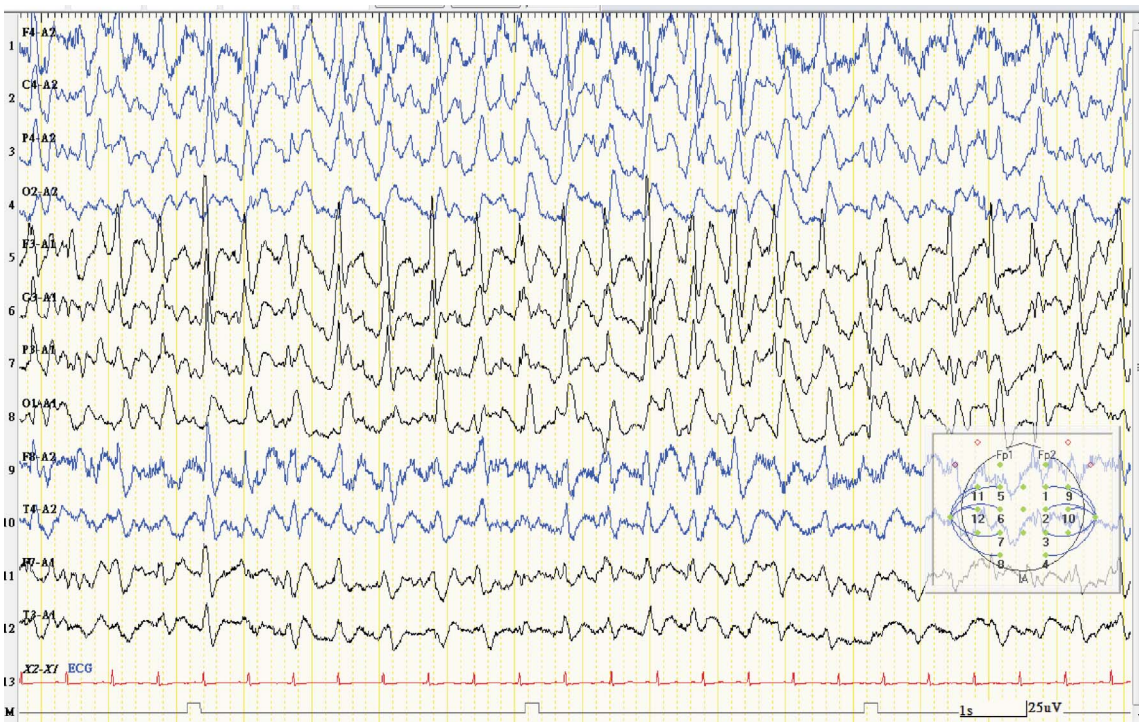

Fig. 2. Emergent EEG showed continuous, generalized periodic epileptiform discharges, ranging from 0.5 to 3 Hz without visible background rhythm. It highly suggested nonconvulsive status epilepticus (NCSE). Severe metabolic encephalopathy was excluded by meanwhile laboratory data. (EEG filter: high/low pass threshold: 35/0.3 Hz).

by cephalosporin as a competitive antagonist of γ-aminobutyric acid (GABA) in brain. GABA is the principal inhibitory neurotransmitter in the brain. Reducing the GABA mediated inhibitory response leads to generate a pro-epileptogenic activity.[16] Other postulated mechanisms for neurotoxicity in cephalosporins involve induction of endotoxins and release of tumor necrosis factor-α, which play a role in septic encephalopathy.[17,18]

The pathogenesis of neurotoxicity in patients with renal insufficiency appears to be medicated by altered pharmacokinetics resulting in rise in circulating cephalosporin concentrations, increased its permeability of the blood-brain-barrier, as well as buildup of toxic organic acids within the cerebrospinal fluid.[19] Neurotoxicity is seen more often in elderly patients, who may have age-related declines in creatinine clearance.

Our case report emphasized on diagnosis of NCSE should be considered in all patients with unexpected changes in mental status during treatment of intravenous cephalosporins, particularly in those with chronic renal disease. Emergent EEG should be indicated to differentiate NCSE from other metabolic encephalopathy, with collateral laboratory data. Once cephalosporin-induced NCSE is highly suspected, immediate withdrawal of cephalosporin is necessary. Continuous EEG monitoring is suggested until the patient's mental status returns to normal and epileptiform discharges shown on EEG resolves. The EEG improvement can corroborate the diagnosis of cephalosporin-induced NCSE after antiepileptic drug administration, though antiepileptic drugs such as phenytoin or valproate may be helpful to treat NCSE but data of prognosis are still lacking from the human studies. Continuous EEG monitoring can assist physicians in both early recognition and accurate management of NCSE in those with high risks (elderly, CKD, prior CNS conditions), while starting to administrate cephalosporins. Nevertheless, NCSE is associated with substantial mortality. The mortality is high in stuporous or comatose patients with an acute medical (systemic or neurologic) cause (27% mortality) as compared with those without acute medical cause (3%) in one retrospective case series.[20] Another prospective study of NCSE reported 52% mortality in critically ill elderly patients, which was correlated with severity of underlying illness.[21]

Finally, NCSE represents a difficult diagnostic and treatment challenge. It has been rarely reported in administration of ceftriaxone. Physicians should be aware of the potential neurotoxic complication in elderly patients with CKD. Further studies are needed to determine the most appropriate treatment paradigms for patients who develop ceftriaxone-induced NCSE.

Conflict of interest

All authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijge.2018.03.016.

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