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CASE REPORT

Ceftriaxone-induced acute reversible encephalopathy in a patient treated for a urinary tract infection

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ABSTRACT

Encephalopathy is a rare side effect of third- and fourth-generation cephalosporins. Renal failure and previous disease of the central nervous system predispose to this neurotoxicity. We describe a case of encephalopathy with generalised triphasic waves in a patient with pre-existent cerebrovascular disease who was treated with ceftriaxone for a urinary tract infection. Early recognition of this complication is relevant given that ceftriaxone discontinuation reverted the neurological syndrome.

KEYWORDS

Ceftriaxone, encephalopathy, neurotoxicity, triphasic waves

INTRODUCTION

Encephalopathy is a rare side effect of third- and fourth-generation cephalosporins. Renal failure and previous central nervous system (CNS) disease have been shown to predispose to this neurotoxicity. We present a case of acute reversible encephalopathy with generalised triphasic waves (TWs) in a patient with pre-existent cerebrovascular disease who was treated with ceftriaxone for a urinary tract infection. The present case illustrates the diagnostic challenges and management of this rare but potentially severe side effect of one of the most commonly prescribed parenteral antibiotics.

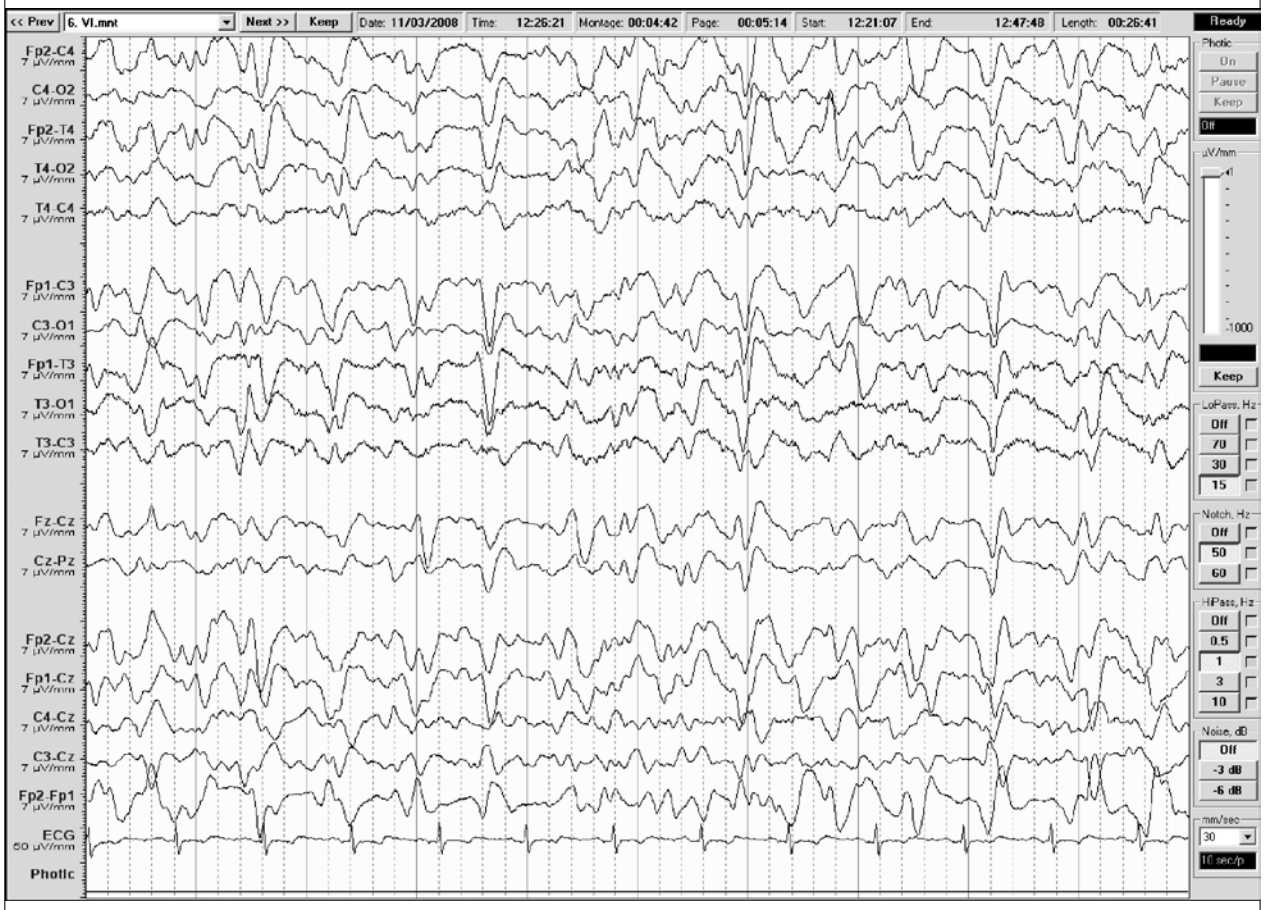
CASE REPORT

A 60-year-old Caucasian female with a chronic urinary catheter presented to our hospital with a four-day history of hypogastric pain and fever. One month earlier, the patient had been diagnosed with acute urinary tract infection and treated with ciprofloxacin. Her medical history included type 2 diabetes mellitus, hypertension, dyslipidaemia and established atherosclerosis (cerebrovascular disease, revascularised coronary heart disease and peripheral artery disease). She was on biphasic isophane insulin (12 IU + 6 IU), amlodipine (10 mg/day), furosemide (20 mg/day), ramipril (10 mg/day), pravastatin (20 mg/day), acetylsalicylic acid (100 mg/day), nitroglycerine (5 mg/day), amitriptyline (25 mg/day) and esomeprazole (20 mg/day). The patient had also been medicated with carbamazepine (400 mg/day) after a single partial seizure occurring six months earlier. An EEG performed then showed slow background activity, with no epileptiform discharges.

In the emergency department the patient was not in acute distress, had no fever, was haemodynamically stable, but dehydrated. C-reactive protein (22.6 mg/l; normal range <3.0) was elevated and acute renal failure (serum creatinine 177 µmol/l [normal range 53.0 to 88.4] and serum blood urea nitrogen (BUN) 10.9 mmol/l; normal range 1.8 to 8.9) was present. Urinalysis revealed bacteriuria and pyuria. The patient was started on ceftriaxone (2 g IV daily) and intravenous fluids. The patient was then admitted to the internal medicine ward. Furosemide and ramipril were suspended. The urine culture was positive for a quinolone-resistant but third-generation cephalosporin-sensitive strain of *Klebsiella pneumoniae*.

After four days of antibiotic coverage, the patient presented altered mental status with progressive apathy and somnolence. No focal neurological signs or convulsive movements were observed. No myoclonic jerks were present. She had no fever and the C-reactive protein

Figure 1. *Periodic generalised TWs, maximally localised over the frontal areas*



Note the persistent background activity, the discharge frequency (medium 1 Hz, always lower than 2 Hz) and the amplitude predominance of phase 2 wave component. Time base 30 mm/sec, amplitude 7 μV/mm.

(14.9 mg/l) and serum creatinine levels (114 μmol/l) were declining. An EEG was performed (*figure 1*) showing high amplitude (200 μV), 1 to 1.6 Hz periodic generalised triphasic waves (TWs), maximally localised over the frontal areas of both hemispheres, although predominantly on the left. The head CT scan did not reveal acute stroke. No abnormalities of liver function tests or in serum electrolytes were present.

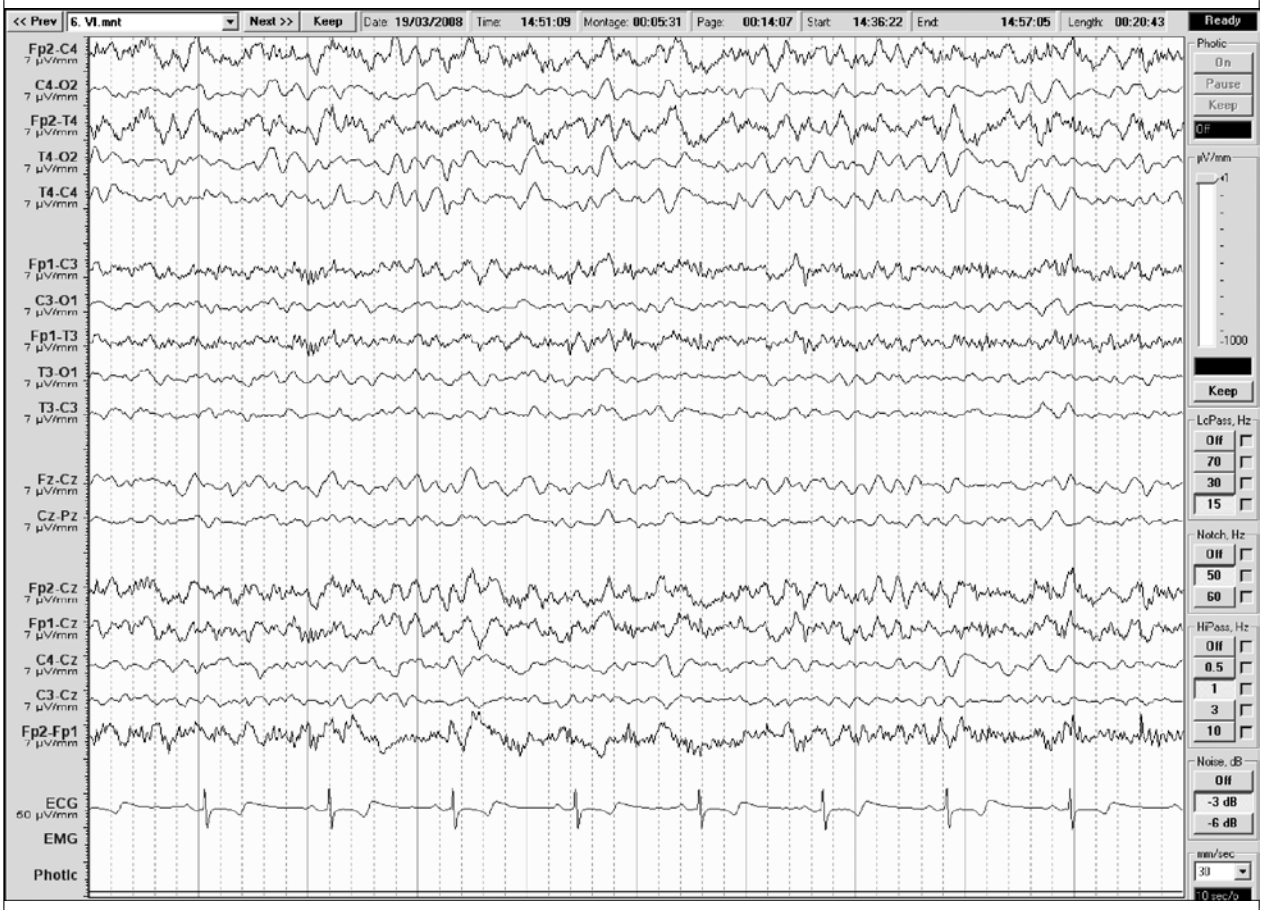
It was unlikely that alcohol withdrawal contributed to the clinical picture given that the patient had no history of alcohol abuse, no seizures, hallucinations or agitation were present, and the symptoms appeared four days after admission. Hypoglycaemia was not detected in capillary glucose monitoring and hyperglycaemia was controlled with insulin administration. Acidosis was absent in repeated arterial blood gas sample analysis. Cerebral hypoxaemia was also unlikely, given normal oxygen saturation in pulse oxymetry and the absence of acute ischaemic lesions in the head CT scan.

A toxic encephalopathy was then considered and ceftriaxone discontinued. The patient's neurological status improved and three days later she was again alert and oriented. A control EEG (*figure 2*) was performed five days later that showed no TWs. A gross asymmetry with respect to the right hemisphere was also noted, possibly related to the cerebrovascular disease. The patient was discharged three days later.

DISCUSSION

Neurotoxicity has been reported with both third-generation and fourth-generation cephalosporins.[1-5] The proposed mechanisms include a decrease in γ-aminobutyric acid (GABA)-mediated inhibition and cephalosporin-mediated release of cytokines. In fact, cephalosporins may decrease GABA release from nerve terminals, increase excitatory amino acid release, and exert a competitive antagonism with GABA.[6] Alternatively, cephalosporin treatment has been proposed to induce endotoxin release, which generates cytokines liberation, such as tumour necrosis factor-α, a proinflammatory cytokine implicated in septic encephalopathy.[7]

Figure 2. *In the EEG performed five days after drug discontinuation, TWs have completely subsided*



A gross asymmetry with respect to the right hemisphere is also noted, possibly related to the cerebrovascular disease. Time base 30 mm/sec, amplitude 7 μV/mm.

Pre-existing CNS abnormalities have been indicated as a risk factor for β-lactams encephalopathy.[8] The patient had a history of cerebrovascular disease and a prior symptomatic partial seizure, which probably accounted for the increased risk of drug-induced encephalopathy. In most published cases of cephalosporin-induced encephalopathy, renal impairment was present. This was also the case in our patient, who presented with acute renal failure, progressively corrected with intravenous fluids and treatment of the urinary tract infection. Excessive dosage has also been shown to be an important determinant of cephalosporin neurotoxicity.[8] Given that no dose-adjustment is required for ceftriaxone in the presence of renal failure with the dose used (2 g IV daily),[9] excessive dosage did not seem to play a role in this case.

Different EEG patterns have been described in association with cephalosporin encephalopathy. Both encephalopathy with TWs and nonconvulsive status epilepticus have been reported and the differential diagnosis between the two conditions may at times be difficult. In this case, several EEG features favoured the assumed pattern of TWs, namely the frequency of discharges lower than 2 Hz, the amplitude predominance of phase 2 wave component, the anterior-posterior lag of phase 2, the absence of associated extra spyke components and the persistence of background activity.

Metabolic encephalopathy, especially hepatic and uraemic, is known to be frequently associated with TWs on EEG.[10] Our patient did not present evidence of liver failure and had only mild and reversible acute renal dysfunction that could not account for the observed encephalopathy. In fact, the temporal association of the encephalopathy induction and resolution with ceftriaxone administration and withdrawal makes this antibiotic highly likely to be responsible for the encephalopathy. Moreover, the temporal pattern is in accordance with previous publications reporting cephalosporin neurotoxicity, with a latency of one to ten days after drug initiation and regression of all neurological symptoms within two to seven days following ceftriaxone treatment suspension.[4]

The use of amitriptyline and carbamazepine most probably did not cause this clinical picture given that the patient

had been taking these medications for a long time and that clinical improvement was observed without its discontinuation.

CONCLUSION

We describe a case of acute ceftriaxone-induced acute reversible encephalopathy in a patient treated for a urinary tract infection. Although this potential side effect of cephalosporin treatment is increasingly recognised, the diagnosis is hampered by the broad differential diagnosis of altered mental state in patients with ongoing infection and multiple medical conditions. This neurotoxicity should be specially considered when the patient has pre-existing CNS abnormalities or renal impairment and an EEG should be performed for diagnosis confirmation. Early recognition of this complication is particularly relevant given that discontinuation of ceftriaxone reverted the neurological syndrome.

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