



Case Report

Nonconvulsive status epilepticus cases arising in connection with cephalosporins



Ibrahim Bora¹, Aylin Bican Demir^{*}, Pinar Uzun²

Uludag University Medical School, Neurology Department, 16059 Görükle, Bursa, Turkey

ARTICLE INFO

Article history:

Received 28 March 2016

Received in revised form 11 April 2016

Accepted 30 April 2016

Available online 20 May 2016

Keywords:

Nonconvulsive status epilepticus

Cephalosporin

Prognosis

Treatment

ABSTRACT

Cephalosporins, particularly cefepime, exert neurotoxic side effects that can lead to status epilepticus. These neurotoxic side effects include myoclonus, dystonic movements, tremor, asterixis, seizure, status epilepticus, encephalopathy, and sometimes coma. Status epilepticus, particularly nonconvulsive status epilepticus (NCSE), is a well-known but unusual complication in patients with altered renal function who were receiving treatment with intravenous cephalosporins, especially cefepime. We reviewed the clinical and electroencephalographic (EEG) characteristics of 7 patients with renal failure who developed consciousness alterations with changes in EEG activity while being treated with cephalosporins. All patients developed renal failure: six patients had chronic renal failure, one patient had acute renal failure, and two patients were administered hemodialysis. Nonconvulsive status epilepticus was observed between 2 and 8 days (average of 5.6 days) after initiation of cephalosporins. Cephalosporins are epileptogenic drugs, especially when used in excessive doses or when renal function is impaired. Critically ill patients with chronic kidney disease are particularly susceptible to cefepime neurotoxicity. Clinical and electrophysiological results of patients guide the diagnosis of NCSE by healthcare providers.

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1. Introduction

Cephalosporins are characterized by a broad antimicrobial spectrum and excellent tissue penetration in clinical practice [1]. They are currently among the most widely used lactam antibiotics for the treatment of serious gram-negative infections. Cephalosporins are grouped into “generations” according to their antimicrobial properties: the first-generation cephalosporins include cefazolin, the second-generation cephalosporins include cefuroxime, the third-generation cephalosporins include ceftazidime, and the fourth-generation cephalosporins include cefepime. Cefepime is often used as the first choice for the treatment of severe infections. Cephalosporins, particularly cefepime, have neurotoxic side effects that can lead to status epilepticus [2,3]. Neurotoxic side effects due to cephalosporins include myoclonus, dystonic movements, tremor, asterixis, seizure, status epilepticus, encephalopathy, and sometimes coma [4]. Status epilepticus, particularly nonconvulsive status epilepticus (NCSE), is a well-known but unusual complication in patients with altered renal function who are receiving treatment with intravenous cephalosporins, especially cefepime [4]. Nonconvulsive status epilepticus

(NCSE) is a condition that may be associated with different levels of altered consciousness without any apparent motor signs. Patients with NCSE exhibit continuous or intermittent electrographic discharges detected by electroencephalography (EEG) [5]. Electroencephalographic recording is crucial for recognizing NCSE. A delay in diagnosis and treatment may be associated with increased mortality or neuronal loss, as well as impaired cognitive and behavioral abilities [6]. Discontinuation of the drug often leads to restoration of neurological function. Nonconvulsive status epilepticus is a rare complication of cephalosporin therapy, with only a few isolated cases reported in the literature.

We reviewed the clinical and electroencephalographic characteristics of 7 patients with renal failure who developed consciousness alterations and changes in EEG activity while being treated with cephalosporins, particularly cefepime.

1.1. Case 1

The first case is ES, a 52-year-old man undergoing hemodialysis for the past 4 years because of stage-III chronic renal insufficiency secondary to focal segmental glomerulosclerosis. He was seen in the nephrology clinic because of a progressive decline in mental status, delirium, agitation, disorientation, and difficulty with cooperation sometimes accompanied by myoclonic jerks. His medical history included hypertension and diabetes mellitus for the past 20 years. He presented with high fever and positive blood cultures for *Staphylococcus aureus* and was

^{*} Corresponding author. Tel.: +90 224 2951723; fax: +90 224 4429177.

E-mail addresses: aylinbican@mynet.com (A.B. Demir), bora@uludag.edu.tr (I. Bora), drpuzun@gmail.com (P. Uzun).

¹ Tel.: +90 224 2951712; fax: +90 224 4429177.

² Tel.: +90 224 2951740; fax: +90 224 4429177.

diagnosed with a urinary tract infection. The patient was initially administered cefazolin at 4 g/day; cefazolin was eventually discontinued, and cefepime treatment was started at 2 g every 12 h. A progressive deterioration in mental status, including delirium, agitation, disorientation, and difficulty in cooperating, developed on the second day of cefepime treatment. Neurological examination revealed no focal neurological deficits. Magnetic resonance imaging of the brain showed atrophy in the right temporo-occipital junction reflecting the sequelae of an old infarction of 1.5×2 cm. Electroencephalography revealed continuous 2- to 3-Hz generalized bi/triphasic sharp waves, which led to a diagnosis of NCSE. Cefepime treatment was discontinued, and 10 mg of diazepam was administered via intravenous injection. Clinical symptoms and EEG findings improved approximately 7 days after discontinuation of cefepime (Fig. 1).

1.2. Case 2

The second case is GK, a 39-year-old woman with ankylosing spondylitis, amyloidosis, and chronic renal failure. She was admitted to the orthopedic clinic because of septic arthritis. Drainage was performed, and treatment with cefepime at 3 g/day was initiated. On the sixth day of cefepime treatment, the patient suddenly stopped speaking and exhibited loss of orientation, increased agitation, occasional laughing, meaningless speech, and progressive impairment of consciousness. Myoclonic jerks were also observed. On the neurological exam, we observed that the patient was confused. Her speech was not meaningful, and she was moving all of her extremities in response to painful stimuli. No focal neurological signs or meningismus was present. Laboratory tests revealed a creatinine level of 6.51 mg/dl with a BUN concentration of 56 mg/dl. The Hgb level was 8.2. The platelet count was 185,000, and the Ca^{++} level was 7.9. Cranial MR imaging and LP analysis were normal. An assessment of EEG activity demonstrated continuous, rhythmic, generalized triphasic 2- to 3-Hz sharp-wave activity. Cefepime was discontinued, and Targocid treatment (400 mg) was initiated twice a

day. Diazepam was administered intravenously. Clinical symptoms and EEG findings improved approximately 5 days after discontinuation of cefepime and administration of diazepam. Electroencephalography demonstrated generalized theta- and delta-wave activity (Fig. 2).

1.3. Case 3

The third case is KI, a 24-year-old woman who was being followed in clinic for chronic renal failure due to lupus nephritis and a 3-year history of hemodialysis. Renal transplantation was performed in September of 2014. Tacrolimus and mycophenolate treatments were initiated after transplantation. Ceftriaxone at 2 g/day was initiated to treat recurrent urinary tract infections. The patient deteriorated on the third day of treatment and presented with three generalized tonic-clonic seizures on the same day. Her consciousness did not improve after the seizures. On neurological examination, the patient was confused and could move her limbs only in response to painful stimuli. The blood level of tacrolimus was measured and was within normal limits. The results of a cranial MRI were normal, and there was no indication of an acute infarct. Electroencephalographic activity was characterized by continuous, rhythmic, generalized 2- to 3-Hz sharp-wave activity. Extensive epileptiform activity was also observed in her EEG results. Ceftriaxone was discontinued. Signs and symptoms of NCSE decreased after diazepam treatment and an infusion of phenytoin; symptoms continued to decline as this treatment paradigm was maintained. Clinical symptoms and EEG abnormalities improved approximately 3 days after discontinuation of ceftriaxone.

1.4. Case 4

The fourth case is VK, a 58-year-old woman who was hospitalized because of chronic renal failure accompanied by mesothelioma, diabetes mellitus, coronary artery disease, and bronchopneumonia. Cefepime was initiated at 4 g/day to treat the bronchopneumonia. On the eighth



Fig. 1. First electroencephalogram showing continuous, generalized, rhythmic sharp- and slow-wave discharges.

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