

Acute Neurological Deficits Caused by Cefipime: A Case Report and Review of Literature

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Abstract- Cefepime (Maxipime) is a fourth-generation cephalosporin commonly used to treat a variety of infections. Its controversial side effect profile is not well appreciated by first-line practitioners. We report a case of urinary tract infection treated with cefepime in a 91-year-old woman. The acute onset of conscious disturbance was noted on the 9th day of cefepime treatment. Computed tomogram and magnetic resonance image of the brain showed no specific findings. The neurological symptoms and signs such as conscious disturbance, ocular bobbing, asterixis disappeared after discontinuation of cefepime. We suggest that physicians should consider cefepime as a possible cause of reversible neurological deficits.

Key Words: Cefepime, Reversible neurological deficit, Negative myoclonus, Bilateral periodic lateralized epileptiform discharges, Magnetic resonance imaging

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INTRODUCTION

Cefepime is used to treat beta-lactam resistant bacteria, and it is mainly prescribed for those who have serious urinary tract infections, skin wounds, and lung infections⁽¹⁾. While it is useful in the treatment of infection, it has neurological side effects⁽²⁻⁴⁾. Though cefepime-induced encephalopathy is documented⁽⁵⁻⁹⁾, its neurological manifestations have not been well described. We present a patient who was initially diagnosed as a stroke and finally proved to be the side effects of cefepime. The patient recovered completely after discontinuation of the medication.

CASE REPORT

A 91-year-old woman, who had a history of the right hip fracture and was in a regular rehabilitation program, was admitted to the medical ward due to high fever and right flank pain. A urinary tract infection was suspected because that urine analysis revealed a presence of white blood cells. A urine sample was cultured and empirical antibiotic therapy of cefepime (2 g every 8 h by intravenous drip) was prescribed under suggestion of an infection expert. The white blood cell count decreased from 15,000/ μ L to 9,000/ μ L and fever subsided after treatment. However, on the 9th day of

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cefepime treatment, the patient became stuporous. Neurologic examination showed that her light reflex (direct/indirect) was impaired and the pupil size were 4.0 mm bilaterally. There was absence of the corneal reflex. The gag reflex was also decreased. Her natural eye position was skewed and accompanied by ocular bobbing. Her vestibulo-oculocephalic reflex was also impaired. The patient remained in a decerebrate posture on pain stimulation. The Babinski sign was dorsiflexed bilaterally. Deep tendon reflexes in all four limbs were increased. Emergency brain computed tomogram and serum biochemistry showed no significant abnormalities.

Two hours later, the respiratory pattern became bizarre, and arterial blood gas analysis revealed respiratory acidosis. The patient was intubated and transferred to the medical intensive care unit (MICU) for close observation. The initial diagnosis was brainstem stroke.

The urine culture disclosed *Pseudomonas aeruginosa*, which was sensitive to the empirical antibiotics. Under the impression of brainstem stroke, we prescribed antiplatelet therapy (clopidogrel once daily). On the second day in the MICU, the patient developed negative myoclonus predominantly at the bilateral forearms and right cheek areas, which preceded convulsions. The negative myoclonus was obvious when the hands were forced to stretch out and was distributed predominantly in the distal phalanges. On the 11th day of cefepime treatment, an electroencephalogram revealed bilateral periodic lateralized epileptiform discharges (Bi-PLEDS) (Fig. 1). We administered phenytoin for treatment of the convulsions, but they did not cease. We discontinued cefepime on the 14th day of cefepime treatment because the UTI was resolved. Four days later, the convulsions and negative myoclonus disappeared. On the 7th day after the discontinuation of cefepime, to our great surprise, the patient became alert.

The results of brain magnetic resonance images (Fig. 2) and carotid duplex and transcranial color-coded duplex ultrasonography, which were performed on the 29th day after discontinuation of cefepime treatment, were all normal. Lumbar puncture was done on the 30th day after the discontinuation of cefepime treatment and revealed insignificant findings as well. The patient was

extubated and discharged from the MICU without neurological deficits. A follow-up electroencephalogram on the 32th day after discontinuation of cefepime treatment showed alpha waves interspersed with rare theta waves (Fig. 3). The patient was discharged from the hospital on the 36th day after discontinuation of cefepime treatment.

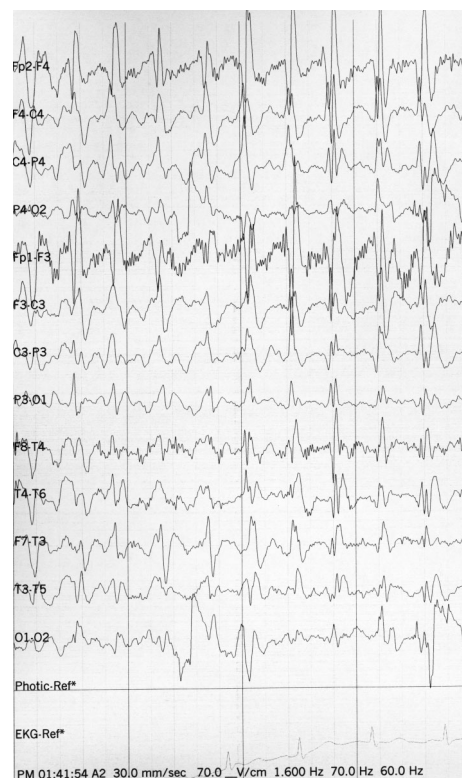


Figure 1. Bilateral periodic lateralized epileptiform discharges at 2-3 Hz with lack of background alpha rhythm.

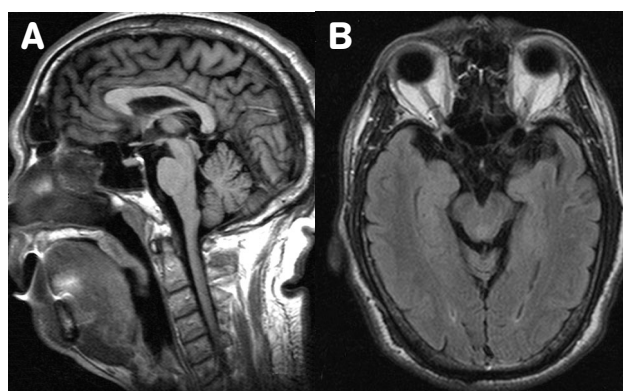


Figure 2. Brain MRI. (A) T1 weighted image, sagittal view. (B) FLAIR.

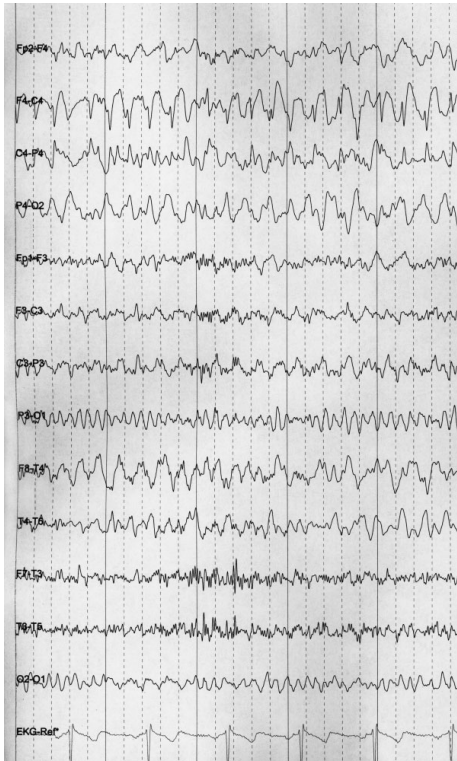


Figure 3. Background activity of alpha waves (8-9 Hz, 10-30(V), is interspersed with rare theta waves.

DISCUSSION

Cefepime, a fourth-generation cephalosporin, is widely used by many internists to treat the toughest infections⁽¹⁻⁴⁾. Nonetheless, its neurotoxicity and side effects are often overlooked^(1,2).

This 91-year-old woman was in good health and had no risk factors for strokes such as hypertension, diabetes mellitus, smoking, or hypercholesterolemia except for old age. Thus, cefepime usage in very elderly patients might be a contributing factor to the neurotoxicity. We initially assumed that the patient's change in consciousness might be an "encephalopathic" event. Differential diagnoses included hypoglycemia, electrolyte imbalance, adrenal insufficiency, hypothyroidism, hyperthyroidism, and hepatic encephalopathy. The electroencephalography change was unique and sometimes reminiscent of central nervous system infection, such as Creutzfeldt-Jakob disease, or other neurodegenerative diseases. However, the

time course, brain MRI findings, and CSF findings did not favor these above possibilities.

Literature related to the side effects of this disorder focused on encephalopathy, seizures, and involuntary movements⁽¹⁻⁹⁾. Common initial manifestations are spatial disorientation, delirium, personality changes, and restlessness. According to Saurina et al.⁽³⁾, neurological disorders with a confused state are frequently encountered in uremic or elderly patients when they are brought to their physicians. The average interval between the onset of symptoms and diagnosis of the disorder was about 3 ± 5 days after cefepime treatment⁽⁵⁻⁷⁾. Among uremic and elderly patients, side effects were usually related to dose variation. Many cases of severe and reversible cefepime-induced encephalopathy have been described in elderly patients. Most of the patients included were either old or in a uremic state with regular hemodialysis^(2-5,9). The leading manifestations of the encephalopathy included convulsive or non-convulsive status epilepticus, characterized by semi-periodic diffuse triphasic waves^(1,5,8,9).

The cefepime dose should be no more than 1 g/day, especially for those with a poor renal function^(3-5,6-8). Our patient had no renal dysfunction except for old age. Whether there is a relationship between aging and developing encephalopathy, or the elderly are prone to developing encephalopathy remain unclear.

Negative myoclonus was observed in our patient and was transient and disappeared after cessation of this antibiotic. It occurred mainly in the distal phalanges of the upper extremities. Its mechanism is still under investigation.

It is reasonable for a doctor to suspect the encephalopathy as a vascular event in the aged person and it is also difficult for physicians to correlate the stroke-like symptoms and side effects of the antibiotics. The mechanism is still unclear, but cefepime's affinity for intracranial vessels, leading to temporary vasospasm, could be a possible explanation.

In summary, our patient presented with transient neurological dysfunction after being treated with cefepime. These reversible cefepime-induced neurological deficits are rare. To determine how cefepime causes neurological deficits will require further studies. We sug-

gest that physicians should regard cefepime as a possible cause of reversible neurological deficits.

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