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CLINICAL REPORT

Cefepime-induced encephalopathy in a COVID-19 patient: a case report

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Abstract
Prolonged neurological symptoms such as "brain fog" and cognitive impairment have occurred after coronavirus disease 2019 (COVID-19) infection. In this report, we describe impaired consciousness caused by cefepime hydrochloride (CFPM) in a patient with cognitive sequalae of COVID-19. A 56-year-old male patient was diagnosed with penile abscess after COVID-19 infection, and a blood culture detected two drug-resistant *Pseudomonas aeruginosa* strains. Therefore, CFPM 2 g × twice/day was administered on day 71 after intensive care unit admission. Approximately 48 h after CFPM administration, the patient showed disturbances in consciousness. Contrast-enhanced computed tomography, magnetic resonance imaging, and spinal fluid examination revealed no obvious abnormalities. Therefore, CFPM-induced neurotoxicity was suspected. CFPM was discontinued and ceftazidime 2 g × three times/day was initiated. The patient's consciousness improved 30 h after the final administration of CFPM. Serum CFPM concentrations were 14.2, 21.7, 21.7, and 11.9 μg/mL on days 1, 2, and 3 after the initiation of CFPM and on the day after CFPM was discontinued, respectively. In conclusion**,** intensivists should pay attention to new neurological symptoms such as CFPM-induced encephalopathy in patients with prolonged neurological symptoms after COVID-19 infection.

Keywords Cefepime · Encephalopathy · COVID-19 · Blood–brain barrier · Blood purification · Chromatography

Introduction

Cefepime hydrochloride (CFPM) may cause neurological symptoms, such as impaired consciousness, myoclonus, and seizures. In this report, we describe a case of impaired consciousness caused by CFPM in a patient with coronavirus disease 2019 (COVID-19). Written informed consent was obtained from the patient and patient's family for the publication of this case report.

Case report

A 56-year-old man (height 170 cm, weight 74 kg) had a history of hypertension, hyperlipidemia, and diabetes mellitus. He developed fever, sore throat, and headache 6 days prior to admission. He was referred to our hospital and was admitted to the intensive care unit (ICU) after testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) using polymerase chain reaction (PCR) and was diagnosed with pneumonia at another hospital. On admission, his consciousness was lucid, with a Glasgow Coma Scale (GCS) score of E4V5M6. The patient's oxygenation capacity deteriorated rapidly, and venovenous extracorporeal membrane oxygenation (VV-ECMO) was introduced after tracheal intubation on day 2 of admission. Pharmacological therapy for COVID-19 included administration of remdesivir, dexamethasone, and anticoagulation with continuous

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heparin administration. On day 15, the patient was weaned off VV-ECMO and extubated on day 19. On days 36 and 38, PCR confirmed the patient was negative for SARS-CoV2. However, ICU management was continued due to prolonged kidney injury, cytomegalovirus enteritis, bacteremia, and penile abscess. Intermittent renal replacement therapy was required twice a week for prolonged kidney injury. Although cognitive deficits improved until day 57, fatigue, mood disorder, and memory impairment were prolonged.

On day 71, two drug-resistant *Pseudomonas aeruginosa* strains were detected in the blood culture, and CFPM 2 g × twice/day was initiated. Blood purification for sepsis and coexisting kidney injury (continuous hemofiltration; blood flow rate, 150 mL/min; filtration flow rate, 1000 mL/h; polymethyl methacrylate [PMMA] membrane) was performed. Before beginning CFPM administration, the patient had a GCS score of E4V5M6, lucid consciousness, and an Intensive Care Delirium Screening Checklist (ICDSC) score of zero. The Medical Research Council (MRC) score improved to 41 points, and rehabilitation included on-bed bicycle ergometer exercises and standing training.

Approximately 48 h after the administration of CFPM, the patient started to show disturbances in consciousness, restlessness, and babbling-like speech. On day 74, the GCS score was E3V2M5 and the ICDSC score was 8. The patient opened his eyes with upward rolling of the eyeballs in response to a call but was unable to follow orders. In addition, the patient occasionally shouted loudly. The cause of the altered consciousness could not be determined using contrast-enhanced computed tomography and magnetic resonance imaging. The efficiency of blood purification was increased due to the possibility of worsening sepsis (hemodiafiltration; blood flow rate, 150 mL/min; dialysate flow rate, 500 mL/min; filtrate flow rate; 1500 mL/h; and PMMA membrane). Spinal fluid examination revealed no obvious abnormal findings, including herpes simplex virus, Cryptococcus, or tuberculosis. C-reactive protein decreased from 10.3 mg/dL on day 70 to 2.5 mg/dL on day 74. In addition, the patient's hemodynamics were stable without the need for catecholamines, and hypoglycemia and hypoxemia did not occur after CFPM administration. Therefore, CFPM-induced neurotoxicity was suspected. On day 75, CFPM was discontinued and ceftazidime 2 g × three times/day was initiated. On day 76, the patient's consciousness improved 30 h after the final administration of CFPM. Communication was possible on day 77, and his consciousness was lucid without delirium (GCS score of E4V5M6 and ICDSC score of 0). Furthermore, bicycle ergometer exercises in bed and training for sitting upright could be performed. On day 78, the patient underwent self-propulsion training in a wheelchair. The patient was discharged from the ICU on day 106. At this time, the GCS, ICDSC, and MRC scores were E4V5M6, 0 points, and 50 points, respectively, and standing training and wheelchair transfer were possible during rehabilitation. On day 341, the patient was transferred to the hospital for rehabilitation.

Thereafter, frozen stored blood samples were assessed using high-performance liquid chromatography for a definitive diagnosis. These samples were taken up to one hour before each scheduled CFPM administration. Serum CFPM concentrations were 14.2, 21.7, and 21.7 μg/mL on days 72, 73, and 74, respectively, then decreased to 11.9 μg/mL on the day after CFPM discontinuation. Based on these results and the clinical course, the patient was diagnosed with CFPM-induced encephalopathy (Fig. 1).

Discussion

CFPM-induced encephalopathy is caused by CFPM inhibition of gamma-aminobutyric acid A receptor, an inhibitory neurotransmitter [1]. The clinical manifestations are diverse and include impaired consciousness, disorientation, myoclonus, nonconvulsive epileptic seizures, convulsions, and aphasia.

The metabolic pathway of CFPM involves renal excretion, and approximately 85% of CFPM is excreted from the kidney in its original form. Therefore, CFPM encephalopathy has been frequently reported in patients with impaired renal function and those undergoing dialysis. Risk factors for CFPM-induced encephalopathy are renal dysfunction, CFPM overdose, critical illness, impairment of the blood–brain barrier (BBB), and old age [2–4].

The onset of CFPM encephalopathy has been reported as 4–5 days after the initiation of CFPM administration [2–4]. However, in this case, the onset of symptoms was observed after only 48 h. Previous studies have reported that the median serum trough CFPM concentration at the onset of encephalopathy was 38 μg/mL [4] and that a serum trough concentration of 22 μg/mL is the threshold for the development of CFPM encephalopathy [5]. In this case, the serum trough CFPM concentration was 21.7 μg/mL on days 74 and 75, during the development of CFPM-induced encephalopathy. Our patient developed the disease earlier and had lower serum concentrations than those reported in previous reports.

COVID-19 has a wide variety of clinical manifestations, including respiratory symptoms, such as pneumonia as well as neurological symptoms such as impaired consciousness and stroke [6]. In a previous report, 84% of patients with COVID-19 and acute respiratory distress syndrome had neurological signs [7]. The pathogenic mechanism has been attributed to direct or indirect damage to the central nervous system (CNS) by COVID-19 [8]. It is possible that SARS-CoV-2 enters the CNS via the neuronal and/or hematogenous route [9]. In addition, the cytokine storm caused by

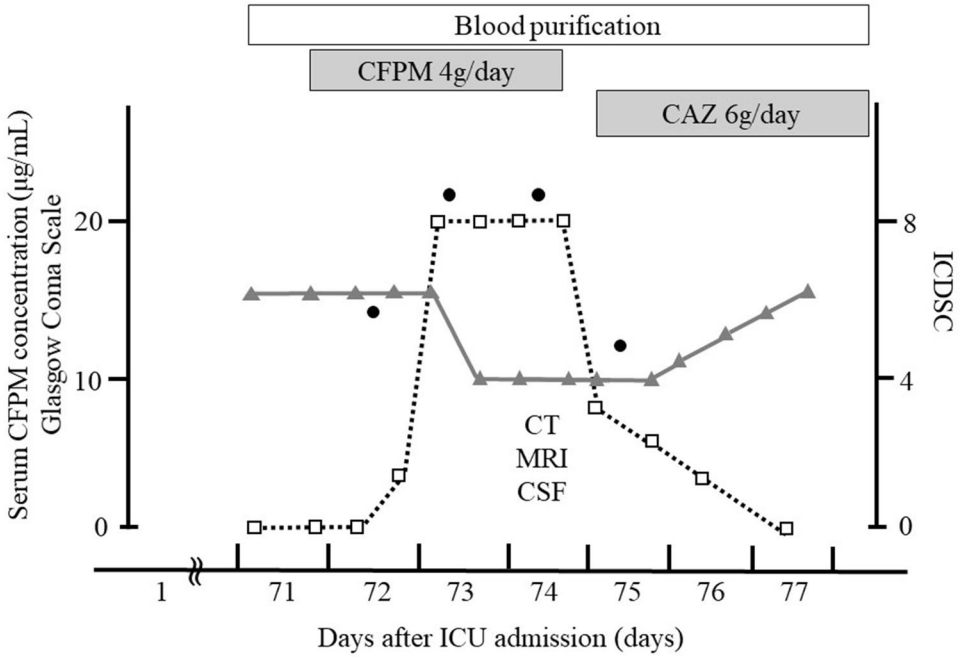

Fig. 1 Clinical course. Gray line and black dashed line indicate alternations in the Glasgow Coma Scale (GCS) and Intensive Care Delirium Screening Checklist (ICDSC), respectively. Black circles indicate serum cefepime hydrochloride (CFPM) concentration. *CT* computed tomography, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *CAZ* ceftazidime

COVID-19 may disrupt the BBB [10]. Several reports have described that neurological symptoms, such as meningitis and encephalopathy, occur after COVID-19 infection, even with a negative spinal fluid SARS-CoV-2 PCR test [11–13]. In fact, a case of pupil dilatation caused by the muscle relaxant rocuronium has been reported in a patient with COVID-19 [14]. Normally, rocuronium does not pass through the BBB. This report suggests that muscle relaxants may cause CNS effects by impairing the BBB due to inflammation and oxidative stress caused by COVID-19.

Prolonged neurological symptoms such as "brain fog" and cognitive impairment have been garnering attention as a "long-COVID syndrome" [15]. Here, chronic neuroinflammation and secondary neurodegenerative processes were considered as potential pathophysiological mechanisms underlying these symptoms [15]. In addition, several studies using fluorodeoxyglucose positron emission tomography revealed brain hypometabolism in long-COVID patients [16]. In our patient, cognitive deficits, mood disorder, and memory impairment were prolonged before the development of CFPM-induced encephalopathy. Therefore, this pre-existing vulnerability of the brain might affect the development of encephalopathies and overall response to CFPM.

There are no specific tests to confirm the diagnosis of CFPM-induced encephalopathy. Discontinuation of CFPM is the diagnostic treatment when suspected and CFPM-induced encephalopathy has been reported to improve within a median of 2 d after discontinuation of administration [4]. In the previous report, dialysis was the treatment of choice for CFPM-induced encephalopathy in only 8% of cases, but the median time to symptom improvement was 1 d in those who underwent dialysis [4]. Because of its low molecular weight, low protein-binding rate, and low volume of distribution, 70% of CFPM can be removed by dialysis within 3 h, and continuous renal replacement therapy is useful, although less efficient than dialysis [17]. In our case, blood purification therapy was performed for sepsis, and the blood concentration of CFPM decreased to 11.9 μg/mL the following day. The patient showed improvement in consciousness 30 h after the discontinuation of CFPM and was able to undergo rehabilitation after 2 days. Blood purification therapy may have contributed to the rapid improvement in CFPM-induced encephalopathy in this case.

In conclusion, we encountered a case of impaired consciousness due to CFPM administration in a patient with cognitive sequalae of COVID-19. Intensivists need to pay attention to new neurological symptoms such as CFPM-induced encephalopathy in patients with prolonged neurological symptoms after COVID-19 infection.

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