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Case report

Encephalopathy induced by high levels of ceftriaxone in the blood and cerebrospinal fluid

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ABSTRACT

Ceftriaxone is commonly used to treat bacterial infections. Encephalopathy is a rare adverse effect of ceftriaxone therapy, and most cases have been diagnosed based on medical history. We report a case of a 73-year-old woman with ceftriaxone-associated encephalopathy, which was confirmed by measuring the ceftriaxone levels in the blood and cerebrospinal fluid. She regularly underwent hemodialysis. She received intravenous ceftriaxone at a dose of 1 g/day for 4 days for enteritis, and mental status began to be disturbed during the therapy. Six days after ceftriaxone discontinuation, her consciousness level rapidly improved. Thus, ceftriaxone-associated encephalopathy was suspected. High ceftriaxone levels in the blood and cerebrospinal fluid were observed while the patient had disturbed consciousness. This case indicated that high ceftriaxone levels in the blood and cerebrospinal fluid were related to development of encephalopathy. The estimation of ceftriaxone levels may be useful for an accurate diagnosis.

Introduction

Ceftriaxone is a third-generation cephalosporin commonly used to treat bacterial infections. Neurologic adverse effects of ceftriaxone are infrequent; however, some cases of encephalopathy have been recently reported in elderly people with end-stage renal disease (ESRD) [1–6]. The exact mechanism whereby ceftriaxone causes encephalopathy remains unclear. High levels of ceftriaxone in the blood and cerebrospinal fluid (CSF) are presumed to cause encephalopathy; however, only a few cases have specifically examined theses biofluids, especially the CSF, in affected patients. Instead, nearly all cases have been diagnosed based on a recent history of ceftriaxone exposure, improvement after its cessation, and exclusion of other causes of encephalopathy. Herein, we describe a case of ceftriaxone-associated encephalopathy in an elderly woman presenting with high levels of ceftriaxone in the blood and CSF.

Case report

A 73-year-old woman was transferred to our hospital with disturbed consciousness. She had hypertension and ESRD and underwent hemodialysis three times a week at another hospital. The patient received amlodipine and telmisartan. Before transfer to us, she also received intravenous ceftriaxone (1 g/day) for enteritis for 4 days and experienced disturbed consciousness. The patient's vital signs were normal, but she showed confused conversations, agitation, and hyperkinesia. Laboratory findings were as follows: white cell count, 3800 cells/μL; hemoglobin level, 10.7 g/dL; platelet count, 3.4×10^4/μL; albumin, 2.9 g/dL; aspartate aminotransferase, 25 U/L; alanine aminotransferase, 10 U/L; blood urea nitrogen, 20.0 mg/dL; creatinine, 7.0 mg/dL; sodium, 135 mEq/L; calcium, 8.3 mg/dL; glucose, 137 mg/dL; and NH3, 35 μg/dL. Analysis of the CSF sample obtained on day 3 at our hospital showed cell counts, protein levels, and glucose levels of 1/μL, 54 mg/dL, and 65 mg/dL, respectively. Head computed tomography and magnetic resonance imaging did not show abnormalities, and an electroencephalogram showed generalized slowing waves. Ceftriaxone-associated encephalopathy was suspected based on the patient's history. Administration of ceftriaxone was terminated after transfer to our hospital and no specific interventions were performed. Her level of consciousness did not improve until day 6. However, on day 7, it quickly improved and returned to the basal levels. The patient was discharged without sequelae. Later, we measured ceftriaxone levels in the reserved plasma and CSF samples obtained during hospitalization. The plasma

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ceftriaxone levels on days 1, 3, 7, and 9 after admission were 218.8, 103.7, 9.5, and 5.0 μg/mL, respectively (Fig. 1). The CSF ceftriaxone levels on days 3 and 9 were 5.9 μg/mL and undetectable, respectively.

Discussion

The clinical course of this patient raises two important issues. First, high ceftriaxone levels in the blood and CSF were observed while encephalopathy continued and the estimation of ceftriaxone levels, especially in the CSF, was useful for the accurate diagnosis. Second, although ceftriaxone does not require a dose adjustment according to renal function, a dose of 1 g/day could induce encephalopathy in an elderly patient with hemodialysis.

Ceftriaxone is usually infused intravenously at a dose of 1–2 g every 12–24 h [7]. After ceftriaxone infusion at a dose of 2 g every 24 h in adults with normal renal function, a plasma trough level of 13–15 μg/mL has been reported [8]. The CSF ceftriaxone level after infusion at 2 g has been reported to be 0.18–1.04 μg/mL [9]. Our case showed that high levels of ceftriaxone in the blood and CSF continued even after cessation of ceftriaxone during disturbed consciousness and that her consciousness improved rapidly when ceftriaxone decreased to the trough level. This clearly indicates that the development of encephalopathy was associated with high ceftriaxone levels in the blood and CSF. The exact mechanism whereby ceftriaxone causes encephalopathy is not completely understood: however, it is presumed to be caused by competitive antagonism of brain γoamiobutyric acid, an inhibitory neurotransmitter in the CSF [10], and increased excitatory amino acids [11]. It was reported that because a CSF/blood ratio of ceftriaxone level and blood brain barrier efflux are different among individuals, monitoring the blood levels of ceftriaxone probably cannot be used to estimate the CSF levels [12]. Therefore, the estimation of ceftriaxone level in the CSF may be more important for accurate diagnosis of ceftriaxone-associated encephalopathy. However, since ceftriaxone level in the CSF has been rarely reported in the affected patients, the critical value is unknown.

Most cases of ceftriaxone-associated encephalopathy occur in elderly people with renal impairments, and receive 2 g or more of ceftriaxone a day [1–6]. It is noteworthy that our patient developed encephalopathy even at a dose of 1 g/day. Since ceftriaxone is eliminated via urinary and biliary excretion, it does not require a dose adjustment according to renal function [7]. However, ceftriaxone is not dialyzed during hemodialysis and the elimination half-life of ceftriaxone was reported to be longer in hemodialysis patients when compared to adults with normal renal function [13]. Moreover, in elderly people, gallbladder contraction decreases and cholestasis is often observed, which can also be related to delayed elimination of ceftriaxone. The protein-unbound, free fraction of ceftriaxone can passively penetrate the blood-brain barrier. This free fraction of ceftriaxone is higher in patients with impaired renal function [14]. In these patients, an accumulation of toxic organic acids or an alteration of pH contribute to impaired active transport of the molecules from CSF to blood [15]. Furthermore, in elderly people, blood-brain barrier permeability is reported to be increased [16]. These factors may increase ceftriaxone levels in the CSF, prompting encephalopathy in elderly people with ESRD.

In summary, the estimation of ceftriaxone levels in the blood and CSF may facilitate an accurate diagnosis of ceftriaxone-associated encephalopathy. Physicians should be cautious about development of ceftriaxone-associated encephalopathy in elderly people with ESRD, even at a dose of 1 g/day.

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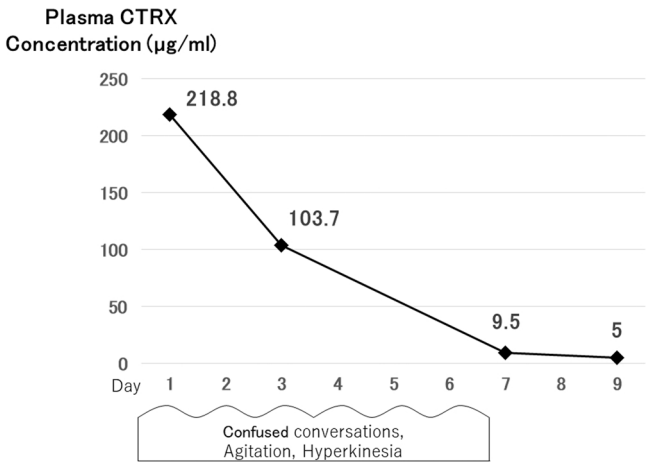

Fig. 1. Patient's clinical course. CTRX, ceftriaxone.

CRediT authorship contribution statement

TM wrote the first draft of the case report. **TM**, **HS**, and **KI** collected and analyzed the data. **HS** and **HN** reviewed the literature. **HN** supervised the manuscript writing, editing, and review. All authors read and approved the final manuscript.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient.

Conflict of interest

The authors declare that they have no conflict of interest.

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