

Case Report

# Choreoathetosis Is a Possible Adverse Event of a Commonly Used Antibiotic

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## Keywords

Choreoathetosis · Cephalosporin · Chronic renal failure · Glutamate

## Abstract

**Background:** Choreoathetosis (CAS) is attributed to a few neuropsychiatric drugs; however, it is scarcely reported with commonly used antibiotics. **Aims:** To present a case of ceftriaxone (CTX)-induced CAS and to perform a literature review. **Setting:** A medical teaching hospital. **Case History:** An 83-year-old female with end stage renal disease was prescribed CTX 2 g/day intravenously and doxycycline (DXC) 200 mg/day orally for the treatment of acute community-acquired systemic infection. CAS developed 3 days after the administration of both drugs. Withdrawal of CTX and DXC yielded complete resolution of the CAS on the following day. Neither neurological adverse events related to DXC use nor pharmacological interaction between DXC and CTX was reported. Therefore, the CAS development was attributed to CTX. **Conclusion:** CTX as well as other  $\beta$ -lactam antibiotics induce glutamate excess in the striatum and cerebral cortex, resulting in neurological hyperexcitability disorders. Dosage adjustment of these antibiotics in relation to the patients' renal clearance is warranted.

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## Introduction

Choreoathetosis (CAS) is an involuntary movement disorder (IMD) characterized by a nonrhythmic throwing, flowing, and twisting movement disorder of one or more limbs. The development of CAS has been attributed to various etiologies, both neurological and systemic disorders, such as genetic and hereditary disorders, cerebrovascular diseases, systemic lupus erythematosus and other connective tissue diseases, hyperthyroidism, hypoparathyroidism, poststreptococcal infection (rheumatic or Sydenham chorea), focal cerebral infection, hyperglycemia, postanoxic and posttraumatic brain injury, etc. [1]. Cases of drug-induced CAS have been seldom reported to date. Apart from neuropsychiatric agents, very few other drugs have been related to its presentation. Here, the author presents the case of a patient of advanced age with end stage renal disease (ESRD) that was complicated by CAS after ceftriaxone (CTX) treatment for acute undifferentiated systemic infection.

## Case History

An 83-year-old female had a long history of essential hypertension, which was eventually complicated with ESRD 8 years earlier. She needed regular hemodialysis (2 sessions/week) to maintain her physiological balance. Her general medical condition had been stable until 5 days prior to the first presentation when she got an acute high-grade fever and malaise without organ-specific symptoms. The initial complete blood count revealed a total white blood cell count of  $4.54 \times 10^3$  cells/ $\mu\text{L}$ , with polymorphonuclear cells 76.6%, lymphocytes 12.8%, monocytes 9.5%, eosinophils 0.7%, and basophils 0.4%. Hemoglobin was 11.5 g/dL with hypochromic and microcytic erythrocytes, and the platelet count was  $178 \times 10^3$  cells/ $\mu\text{L}$ . Blood sugar was 133 mg/dL. Blood urea nitrogen was 69.7 mg/dL. Calcium was 10.5 mg/dL and phosphorus was 4.5 mg/dL. All of the above-mentioned laboratory results were comparable with the previous ones recently done during several follow-up visits. Two specimens of blood culture for identification of causative organism were taken but the results were pending. The attending physician prescribed intravenous CTX 2 g/day combined with oral doxycycline (DXC) 200 mg/day as the primary antimicrobial agents. Three days later, the patient was brought back to the emergency department with subacute bilateral and symmetrical CAS involving both upper and lower limbs, which reached its peak and attained a plateau within 8 h from the onset. The abnormal movement, however, was reported to totally disappear when she was asleep. Her consciousness and other neurological functions remained totally unaffected. At this visit, her febrile illness had gone, and the results of the repeated blood chemistry and renal function tests were also unremarkably changed from the initial ones. A magnetic resonance image of the brain revealed only moderately diffused and appropriate-for-age cerebral atrophy with no significant intracranial abnormality. Because of the presence of nonlateralized IMD, the improvement of the infective condition, and the proximity of antimicrobial agent exposure to the onset of CAS, a diagnosis of drug-induced IMD was provisionally made after completing neurological evaluation. Therefore, both CTZ and DXC were withdrawn immediately. The CAS slowly diminished, and disappeared completely on the following day. The blood cultures for bacteria collected at the first presentation also showed no organism growth eventually.

## Discussion

CTX is a widely used  $\beta$ -lactam antibiotic with a broad bacteriocidal spectrum over both gram-positive and gram-negative bacteria. While its elimination half-life ( $T_{1/2}$ ) is 6–9 h in normal subjects, it prolongs to 16.6 h in patients with ESRD: creatinine clearance (CCr)  $<5$  mL/min/1.73 m<sup>2</sup> [2]. Although CTX is dialyzable, its blood concentration achieves the bacteriocidal range during hemodialysis independent of CCr [2]. As it has a moderately longer  $T_{1/2}$  and is not affected by hemodialysis, the administration of a once-daily dose of CTX is rational and practical to eradicate susceptible organisms in patients with severely impaired renal function. Common adverse events attributed to CTX use are skin rash, respiratory system disorders, generalized physical discomfort, and gastrointestinal disorders, whereas nervous system involvement has rarely been mentioned [3]. DXC is a tetracycline-class broad spectrum antibiotic for bacteria and protozoa. Its common undesired effects included diarrhea, nausea, vomiting, erythematous skin rash, and photosensitivity. Unlike CTX, no neurological adverse reaction related to DXC administration has been reported.

Many forms of drug-induced IMD can be experienced such as parkinsonism, tremor, and dystonia, but rarely CAS. Only a few neuropsychiatric medicines have been reported to induce CAS, such as phenytoin [4], lithium [5], and pemoline [6], but CTX is scarcely included in this association in English literature reviews. Only 1 previous report of 4 cases of CTX-induced CAS in ESRD patients by Sato et al. [7] was identified. Apart from the mentioned CAS cases which represent subcortical striatal neuronal disorder, a few cases of reversible encephalopathy after withdrawal of CTX have been reported [8, 9]. Moreover, 1 case and a further 2 cases of nonconvulsive status epilepticus attributed to treatment with CTX have been reported and summarized [10]. Interestingly, a case of recurrent nonconvulsive status epilepticus after re-exposure to CTX was also documented [11]. These case reports support the neurotoxicity associated with CTX use.

The neural mechanisms underlying drug-induced CAS have not been well understood. Impaired  $\gamma$ -butyric acid (GABA) modulation, cytokine release (i.e., tumor necrosis factor- $\alpha$ ) regulated by bacterial endotoxin, and interestingly, the excess of glutamate, a neuroexcitotoxic neurotransmitter, have been hypothesized [2]. Excessive glutamatergic neurotransmitter expression was associated with nigrostriatal neuronal damage found in an experimental rat model of Parkinson disease [12]. Hence, the imbalance of excitatory and inhibitory motor control pathways within the striatum may cause the occurrence of IMD. Furthermore, not only subcortical striatal neurons but also cortical neurons were affected by glutamate excess in an animal model of Huntington disease [13]. Thus, glutamate exerts a significant influence on both cortical and subcortical striatal neurons, which leads to a variety of neurological disorders such as seizure, encephalopathy, and IMD in its marked excess within the brain. Since the clinical presentation in the reported case was typical for IMD in which the symptoms totally disappeared during sleeping, and the patient was considered to have no intracranial infection as she had clear consciousness throughout both presentations, neither seizure disorder nor central nervous system infection was likely.

The case reported here is that of a patient of advanced years with a long history of ESRD receiving comedication of CTX and DXC for the treatment of acute systemic infection, in which bacterial or rickettsial infection was likely (an endemic infection in our region). There was no pharmacokinetic interaction between CTX and DXC in the author's review of the previous publications. Therefore, in this case it is possible that CTX contributed to the development CAS. The rapid resolution and disappearance of CAS after CTX withdrawal supports the temporal association between CTX use and the development of CAS in otherwise normal

laboratory and neuroimaging studies. The temporal relation of neurotoxicity associated with cephalosporin was reported to have a latency of 1–10 days after exposure and to resolve 2–7 days after withdrawal [8]. The severely impaired CCr alters the drug's pharmacokinetic profile and potentiates its accumulation to exceed the therapeutic level, which never occurs in normal subjects. Therefore, it is noteworthy to remember this possible adverse reaction in extremely elderly patients with chronic kidney disease, even when a regular dosage of CTX is prescribed [8–10]. Notably, it is possible that not only CTX but also other  $\beta$ -lactam antibiotics exert the class effect of this adverse event [14]. Dosage de-escalation based on CCr is crucial for all medicines in the treatment of severe renal impairment patients.

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### Statement of Ethics

The manuscript was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (Certification No. 59-141-14-1). A signed consent form was obtained from the patient.

### Disclosure Statement

The author has no conflict of interest to declare.

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Sathirapanya: Choreoathetosis Is a Possible Adverse Event of a Commonly Used Antibiotic

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