Journal of the Neurological Sciences 396 (2019) 33–35

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Opsoclonus-myoclonus-encephalopathy induced by cefepime

ARTICLE INFO

Keywords:
Cefepime
Neurotoxicity
Opsoclonus
Myoclonus
Encephalopathy

Dear Editor,

Cefepime is an intravenous broad-spectrum cephalosporin widely used in clinical practice. Cephalosporins might produce reversible neurotoxicity due to gamma-aminobutyric acid (GABA) receptor antagonism [1], particularly when administered during renal dysfunction [2,3]. Cefepime-induced neurotoxicity is associated with myoclonus and other hyperkinetic movements, seizures and non-convulsive status epilepticus (NCSE), with concomitant mental status changes ranging from mild encephalopathy to coma [2,3].

Opsoclonus encompasses high-frequency, irregular, multi-directional saccadic oscillations without intersaccadic interval. Opsoclonus is mediated by abnormal inhibition of brainstem burst neurons that generate saccades [4]. In adults, opsoclonus has been described in association with myoclonus, ataxia and/or encephalopathy during autoimmune parainfectious or paraneoplastic brainstem encephalitides [5]. Here, we present a case of cefepime-induced opsoclonus-myoclonus-encephalopathy.

A 70-year-old woman without significant history presented with severe headache. Neurological examination was normal but investigations revealed a small subarachnoid hemorrhage and a right vertebral artery aneurysm that was immediately coiled. Four weeks later, she had persistent, unexplained delirium. CSF analysis revealed 3097 red blood cells/mm^3, 120 white blood cells/uL (95% lymphocytes), 67 mg/dL of glucose and 270 mg/dL of total protein. She was empirically started on intravenous vancomycin and cefepime for possible meningitis. Cefepime was administered at two grams every eight hours given normal renal clearance.

Three days after antibiotic initiation, her mental status deteriorated to coma and she developed opsoclonus and multifocal stimulus-sensitive myoclonus (Video 1). Imaging studies were unremarkable. Continuous video-EEG monitoring demonstrated a generalized, 2–3 Hz triphasic wave pattern, maximal in bifrontal derivations. Some triphasic waves had sharp morphology but no electrographic seizures were identified (Fig. 1, Video 1). Following the administration of one milligram of intravenous lorazepam, there was progressive attenuation and complete resolution of the triphasic pattern, which was replaced by generalized slow wave activity with mixed theta-delta frequency (Fig. 1).

Levetiracetam was added at 500 mg twice daily given the previously-evidenced suspicious configuration of some triphasic waves. Yet, her condition did not improve despite sustained resolution of the triphasic pattern. CSF cultures were reported negative, antibiotics were discontinued and her mental status progressively improved to somnolence three days later. Levetiracetam was discontinued, opsoclonus resolved and there were occasional lower extremity myoclonic movements. Two weeks later, she was alert and normally interactive with no residual myoclonus (Video 1).

Cefepime neurotoxicity commonly presents with encephalopathy and myoclonus [2,3]. The high doses used to empirically treat suspected meningitis after a recent brain insult in an elderly woman probably predisposed to toxicity despite normal renal clearance. Though this patient had a probable adverse reaction to cefepime (Six points in the Naranjo scale) [6], the inflammatory leptomeningeal process antedating cefepime administration might have contributed as well.

Most EEG patterns during cefepime-induced encephalopathy include triphasic waves overlying diffuse background slowing or a continuous triphasic wave pattern as seen in this case [2,3]. Even though the dramatic and sustained response to low-dose lorazepam in this patient might be considered atypical for generalized NCSE at the stage depicted in the corresponding EEG recordings (Fig. 1A), benzodiazepine-responsive triphasic waves might be seen in both non-epileptic encephalopathies and generalized NCSE. Although triphasic waves might be considered non-specific markers of cortical hyperexcitability during cefepime neurotoxicity, continuous video-EEG monitoring is still paramount to exclude NCSE in these patients [2,3].

Consistent with previous series, myoclonic movements in this patient were multifocal and stimulus-sensitive. Cefepime-induced myoclonus can be of both cortical and subcortical origin. In fact, the pre-

https://doi.org/10.1016/j.jns.2018.10.028
Received 8 October 2018; Received in revised form 30 October 2018; Accepted 30 October 2018
Available online 01 November 2018

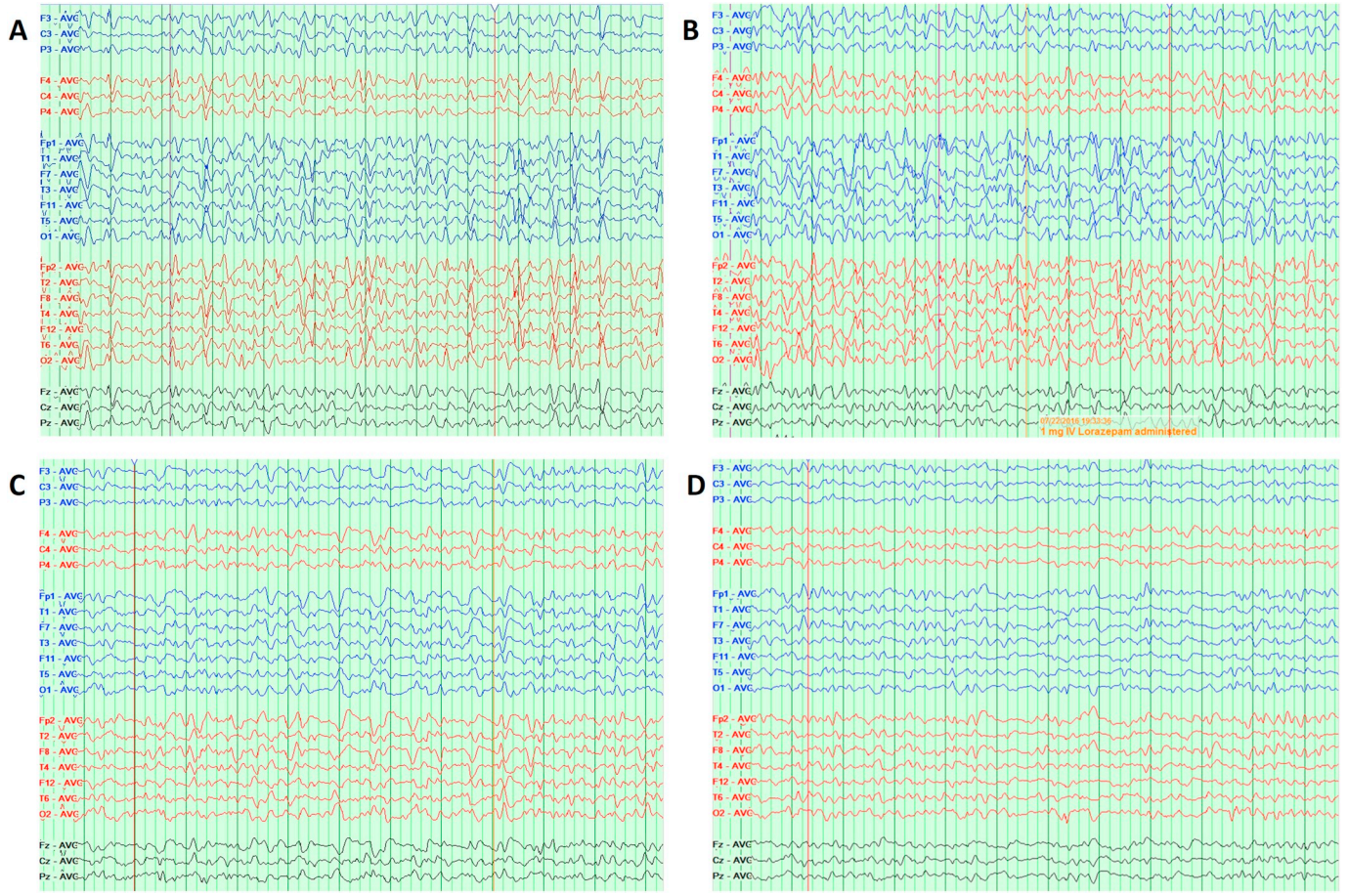

Fig. 1. Scalp electroencephalographic recording examples in this patient with cefepime neurotoxicity. EEG activity was recorded with scalp electrodes positioned according to the 10–20 international system. Signals from average referential montage recorded at a sample rate of 500 Hz, high frequency filter of 70 Hz and low frequency filter of 1 Hz are depicted. (A) Generalized 2–3 Hz triphasic wave pattern with maximal amplitude in anterior head regions. (B) Following the administration of 1 mg of intravenous lorazepam, there was progressive attenuation of the triphasic wave pattern (C) (half-an-hour later), which was then replaced by mixed-frequency diffuse theta-delta slow wave activity with occasional low-amplitude triphasic waves. (D) (one hour later).

dominant involvement of facial, periocular and jaw muscles that has been described in some of these patients would suggest a brainstem origin [2,3,7].

Ocular movement abnormalities are rarely described in association with cephalosporin toxicity. For instance, an oculogyric crisis in a seven-year-old child was attributed to cefixime, a third-generation cephalosporin [8]. Though abnormal ocular movements have not been reported during cefepime neurotoxicity, brainstem hyperexcitability could predispose to abnormal saccadic oscillations and opsoclonus akin to what occurs in autoimmune brainstem encephalitides [4,5].

The opsoclonus, myoclonus and encephalopathy observed in this patient could be explained by widespread neurological hyperexcitability due to reversible GABA receptor antagonism [1]. Thus, cefepime neurotoxicity should be suspected in patients with opsoclonus-myoclonus-encephalopathy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2018.10.028.

Acknowledgments

The authors thank the patient and her family. The authors also thank Drs. Nicole Beaton and Manuel Melo-Bicchi, neurology residents at the Jackson Memorial Hospital/University of Miami School of Medicine program for the care provided to this patient and their assistance in data collection. This case was presented at the Challenging Case Rounds at the 2017 Pan American Parkinson's Disease and Movement Disorders Congress in Miami, Florida, USA.

Declarations of interest

None.

References

[1] M. Sugimoto, I. Uchida, T. Mashimo, et al., Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins, Neuropharmacology 45 (2003) 304–314.
[2] L.E. Payne, D.J. Gagnon, R.R. Riker, et al., Cefepime-induced neurotoxicity: a systematic review, Crit. Care 21 (2017) 276.
[3] J.E. Fugate, E.A. Kalimullah, S.E. Hocker, S.L. Clark, E.F. Wijdicks, A.A. Rabinstein, Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy, Crit. Care 17 (2013) R264.
[4] A.G. Shaikh, S. Ramat, L.M. Optican, K. Miura, R.J. Leigh, D.S. Zee, Saccadic burst cell membrane dysfunction is responsible for saccadic oscillations, J. Neuroophthalmol. 28 (2008) 329–336.
[5] T. Armangue, L. Sabater, E. Torres-Vega, et al., Clinical and immunological features of opsoclonus-myoclonus syndrome in the era of neuronal cell surface antibodies, JAMA Neurol. 73 (2016) 417–424.
[6] C.A. Naranjo, U. Busto, E.M. Sellers, et al., A method for estimating the probability of adverse drug reactions, Clin. Pharmacol. Ther. 30 (1981) 239–245.
[7] S. Khasani, Cefepime-induced jaw myoclonus, Neurology 84 (2015) 1183.
[8] E. Bayram, M.T. Bayram, S. Hiz, M. Turkmen, Cefixime-induced oculogyric crisis, Pediatr. Emerg. Care 28 (2012) 55–56.

Journal of the Neurological Sciences 396 (2019) 33–35

Karlo J. Lizarraga[a,b,*], Deborah O. Heros[a], David Adams[a], Anthony E. Lang[b], Andres M. Kanner[a]

[a] *Department of Neurology, Jackson Memorial Hospital, University of Miami School of Medicine, Miami, FL, USA*

[b] *The Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada*

E-mail address: karlo.lizarraga@gmail.com (K.J. Lizarraga).

* Corresponding author at: Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Division of Neurology, University of Toronto, 399 Bathurst Street, McL 7-402, Toronto, ON M5T 2S8, Canada.