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Usefulness of bilateral bispectral index (BIS) monitoring in a comatose patient with myoclonic status epilepticus secondary to cefepime

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ABSTRACT – *Background*. Status epilepticus, particularly non-convulsive status epilepticus (NCSE), is a frequent complication in patients with altered renal function receiving treatment with intravenous cefepime. To the best of our knowledge, we report the first case, illustrated by video-EEG, of a critically ill patient receiving treatment with cefepime who developed an episode of confirmed symptomatic myoclonic status epilepticus (MSE). *Methods*. Case report and video-EEG. *Results*. A 60-year-old man, who had received a liver transplant due to alcoholic cirrhosis one year ago, was admitted to our intensive care unit due to septic shock. Computed tomography revealed a prostatic abscess as cause of his sepsis. On Day 27, a respiratory infection due to *Pseudomona aeruginosa* was diagnosed, and treatment with intravenous cefepime (2 g/8 hours) was initiated. On Day 32, his mental status deteriorated and he developed inattention, a reduced level of consciousness, and multifocal and generalised continuous myoclonic jerks. A video-EEG study was compatible with the diagnosis of symptomatic MSE. On Day 35, cefepime was stopped and general anaesthesia with midazolam was started in order to achieve a faster clinical improvement. We used the BIS-Vista^{TM} monitor to guide general anaesthesia and detect potential episodes of NCSE. On Day 40, an EEG confirmed the existence of moderate diffuse encephalopathy. Finally, the patient died as a consequence of severe heart failure. *Conclusions*. Cefepime may be a cause of MSE in non-anoxic

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comatose patients. Clinicians should be aware of this possibility when evaluating comatose patients on cephalosporin therapy in order to establish a correct diagnostic approach and accurate prognosis. [*Published with video sequences*]

Key words: bilateral bispectral index, cefepime, continuous EEG monitoring, myoclonic status epilepticus, drug-induced myoclonus

Status epilepticus, particularly non-convulsive status epilepticus (NCSE), is a well-known complication in patients with altered renal function receiving treatment with intravenous cefepime (Dixit *et al*., 2000; Martínez-Rodríguez *et al*., 2001; Chatellier *et al*., 2002; Fernández-Torre *et al*., 2005). In addition, neurotoxic side effects due to cefepime include a broad spectrum of clinical manifestations such as myoclonus, dystonic movements, tremor, asterixis, and coma (Grill and Maganti, 2008). Recently, some authors have emphasized the importance to keep in mind the fact that cefepime neurotoxicity may clinically mimic post-anoxic coma with myoclonic status epilepticus (MSE) (Hocker and Rabinstein, 2011).

To the best of our knowledge, we report the first video-electroencephalogram (v-EEG) study of a critically ill patient receiving treatment with cefepime who developed an episode of profound stupor associated with multifocal facial, trunk, and limb jerks, compatible with the diagnosis of confirmed symptomatic MSE (Foreman and Hirsch, 2012). In addition, we emphasize that the latest bilateral bispectral index (BIS)-Vista™ monitor may be helpful in managing profound sedation and response to antiepileptic treatment in the absence of continuous EEG monitoring (CEEG).

Case study

A 60-year-old man, who had received a liver transplant due to alcoholic cirrhosis one year ago, was admitted to our intensive care unit (ICU) because of septic shock, secondary to urinary tract infection. He was receiving tacrolimus (2 mg/12 hours) as a maintenance immunosuppressive regimen. He had a history of chronic renal failure (CRF) and recurrent renal colics. Computed tomography revealed a prostatic abscess as cause of his sepsis. In the following days, his hospital stay was complicated by aggravation of his CRF, hepatic abscess, lung atelectasis, and severe critical illness polyneuropathy. During this period, the patient was receiving treatment with tacrolimus (1.5 mg/24 hours) and he remained awake, oriented, and cooperative. On Day 27, he presented with fever and hypoventilation in both lungs. A respiratory infection due to *Pseudomona aeruginosa* was diagnosed, and treatment with intravenous cefepime (2 g/8 hours) was initiated. On Day 32, his mental status deteriorated and he developed inattention, a reduced level of consciousness, and multifocal and generalised continuous spontaneous and stimulus-induced myoclonic jerks involving the face, limbs, and trunk. Although the patient's serum tacrolimus level was within normal limits, these symptoms were attributed to tacrolimus neurotoxicity. Magnesium levels were also normal. Magnetic resonance imaging of the brain was unremarkable. Laboratory studies showed a creatinine level of 1.81 mg/dL, blood urea nitrogen of 134 mg/dL, and a biochemical cholestatic pattern. Over the next two days, since he did not experience any clinical improvement despite the reduction of tacrolimus dose, intensivists requested an EEG evaluation. During that period, the values of creatinine varied from 1.6 to 1.93 mg/dL. The v-EEG showed continuous generalised, rhythmic spikes, and spike-wave and sharp slow-wave complexes at 2.5 Hz (*figure 1A*). Epileptiform discharges were associated with prominent myoclonia, in keeping with the diagnosis of symptomatic MSE (*see video sequence*). Treatment with levetiracetam (750 mg/12 hours) and clonazepam (8 mg/24 hours) was started and tacrolimus was stopped and replaced by cyclosporine (300 mg/24 hours). Despite the onset of antiepileptic treatment and withdrawal of tacrolimus, MSE persisted in the following 48 hours. During these days, two consecutive v-EEGs did not reveal any changes. The administration of an intravenous bolus of 4 mg of midazolam during the second v-EEG temporally abolished epileptiform activity and motor manifestations (*figure 1B*). On Day 35, cefepime toxicity was suspected. Cefepime was stopped and general anaesthesia with midazolam was started in order to achieve a faster clinical improvement. Since we do not perform CEEG in our hospital, we used the BIS-Vista™ monitor in order to guide general anaesthesia and detect potential episodes of NCSE. We recently tested the utility of this system in the management of focal NCSE (Fernández-Torre and Hernández-Hernández, 2012). BIS-Vista (Aspect Medical Systems Inc., Norwood, MA) version 3.00 sensors were bilaterally placed on the forehead according to the manufacturer's guidelines. We correlated EEG activity and BIS values after midazolam administration in order to optimise the sedation level. Thus, we observed complete control of epileptiform activity with BIS values near to 50. Moreover, a significant modification of the colour density spectral

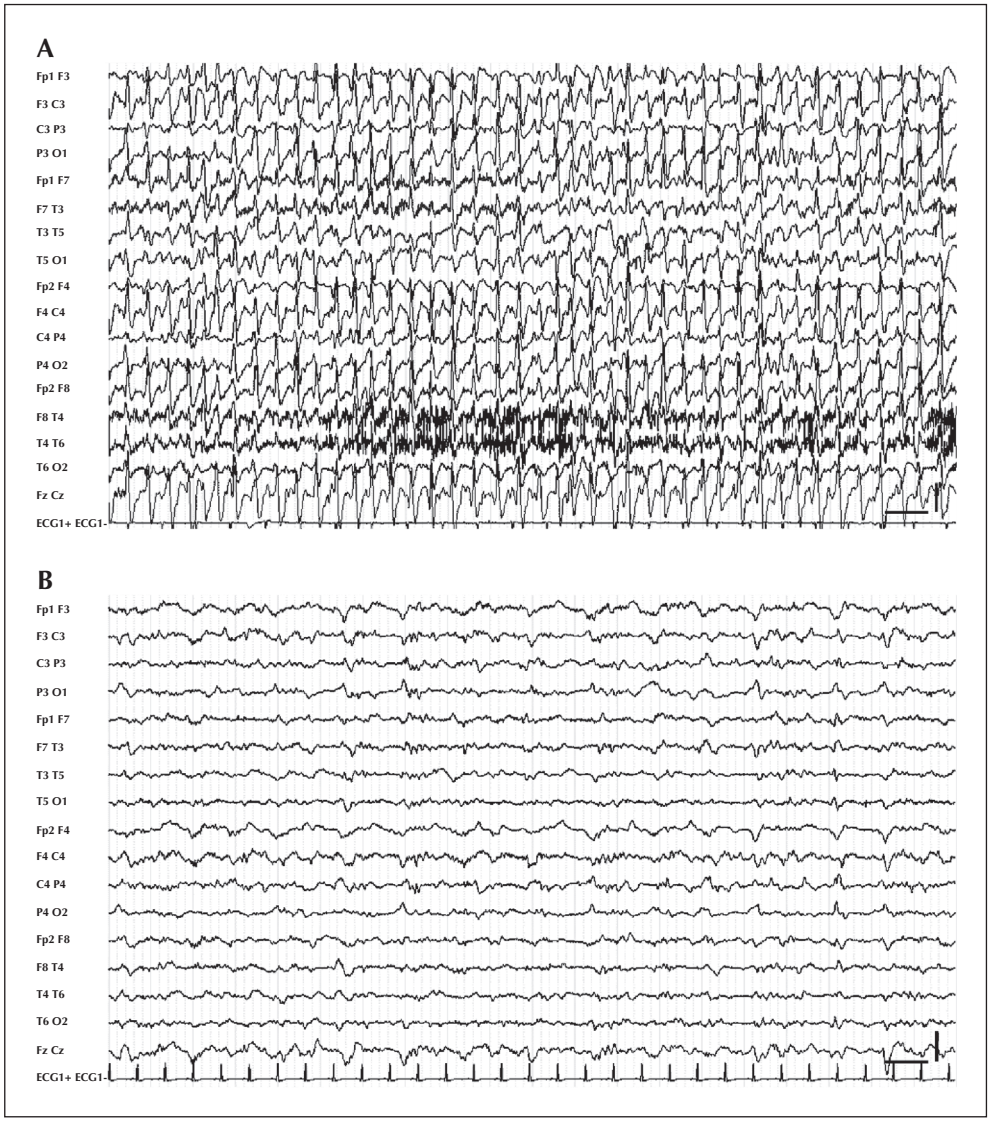

Figure 1. A) Digital EEG showing the existence of continuous generalised epileptiform discharges compatible, in the clinical context, with myoclonic status epilepticus (MSE); B) Administration of an intravenous bolus of 4 mg of midazolam during the second v-EEG recording temporally abolished epileptiform discharges, causing a cessation of motor manifestations.
LF: 0.53 Hz; HF: 35 Hz; NF: 50 Hz; vertical bar: 100 μV; horizontal bar: 1 second.

array (CDSA) was observed (*figure 2*). During the subsequent days, the patient remained sedated and the analysis of CDSA showed a control of MSE. On Day 40, an EEG carried out during working hours confirmed the existence of moderate diffuse encephalopathy without epileptiform activity. Unfortunately, a few days later, the patient died as a consequence of severe heart failure.

Discussion

There are two important points that emerge from this study: i) cefepime may cause MSE in non-anoxic subjects, thus, to the best of our knowledge, this is the first case illustrated by v-EEG, of a critically ill subject receiving treatment with cefepime who developed an episode of definite symptomatic MSE; and ii) the latest bilateral bispectral index (BIS)-Vista^{TM} monitor may be helpful in order to guide general anaesthesia for status epilepticus when CEEG is not available. Of note, CDSA was easy to interpret at the bedside and useful for monitoring the recurrence of epileptiform activity and detection of potential episodes of NCSE.

MSE has been described in generalised epilepsy syndromes, progressive neurodegenerative diseases, toxic-metabolic encephalopathies, and following hypoxic-anoxic brain injury (Kirac *et al.*, 2013). The

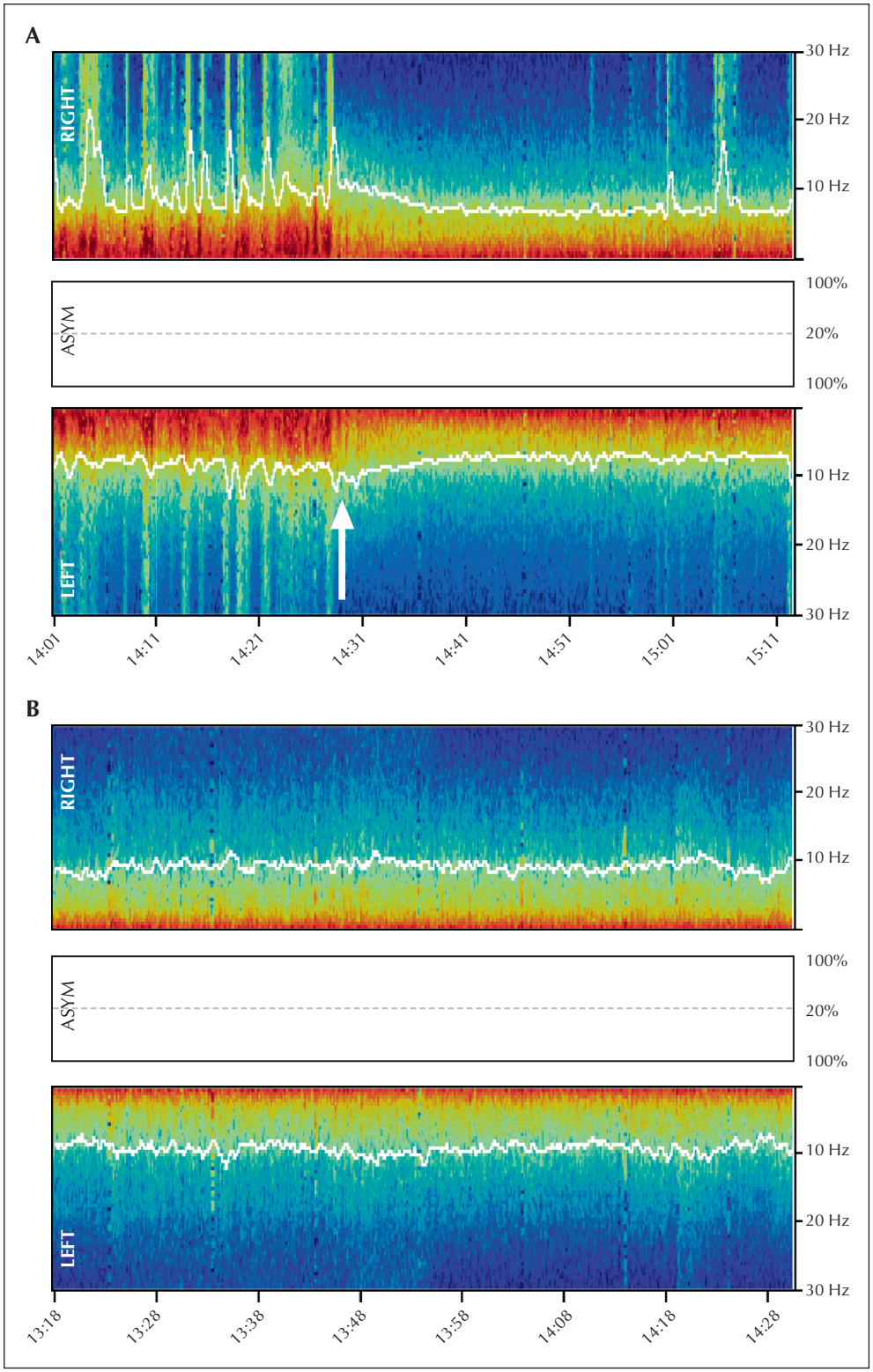

Figure 2. A) Colour density spectral array (CDSA) revealing the control of myoclonic status epilepticus (MSE) during the sedation with intravenous midazolam (white arrow); B) Aspect of the CDSA following the resolution of MSE.
The CDSA applies fast-Fourier transformation to convert raw EEG data into a time-compressed and colour-coded display for frequencies between 0 and 30 Hz, with blue representing low power, and green, yellow and red representing successively higher power.

demonstration that cefepime can cause MSE is important since it may have diagnostic and therapeutic consequences in the evaluation of comatose subjects with myoclonus admitted to the ICU. Obviously, the clinical history is crucial in the evaluation of comatose patients with MSE. It is not unusual to doubt the existence of hypoxic or hypotensive complications in critically ill subjects. This point is crucial when one makes a decision regarding the aggressiveness of treatment and prognostication (Hocker and Rabinstein, 2011). It is widely known that the prognosis of acute MSE after cardiac arrest is poor, and intensive treatment does not modify outcome at all. However, the occurrence of MSE in comatose subjects with pluripathology might suggest a reversible and potentially benign toxic, metabolic or toxic-metabolic cause and, therefore, be associated with favourable evolution. In addition, in our case, the existence of a concomitant septic encephalopathy could have contributed to stupor and jerks (Wilson and Young, 2003).

Myoclonus is frequently reported as a neurological complication of cefepime therapy, however, the majority of studies do not mention the origin of the myoclonus (*i.e.* cortical *versus* subcortical). Myoclonic activity of cortical origin has been described in subjects receiving treatment with diverse cephalosporins (Uchihara and Tsukagoshi, 1988; Chatellier *et al*., 2002; Kirac *et al*., 2013). In a recent study, the existence of continuous epileptiform discharges was five-fold more frequent in patients treated with cefepime than in subjects under treatment with meropenem (Naeije *et al*., 2011). These results suggested that cefepime may be an independent risk factor for epileptiform discharges. The potential epileptogenic side effect of beta-lactam antibiotics is widely known and is secondary to an aminobutyric acid (GABA)-mediated mechanism (Grill and Maganti, 2008). Cephalosporins bind competitively to GABA receptors and this could explain the greater potential for neurotoxicity compared to other beta-lactams. Sugimoto *et al*. (2003) reported that GABA-A receptor blockade was observed *in vitro* and *in vivo* with seven commonly used cephalosporins, including cefepime.

It is important to bear in mind that triphasic waves of toxic and metabolic encephalopathies are frequently indistinguishable from EEG patterns observed in NCSE (Fernández-Torre, 2006; Kaplan and Birbeck, 2006; Fernández-Torre, 2007). Common metabolic and toxic encephalopathies include hepatic and renal insufficiency and drug intoxication. Confusional states have been described with lithium, baclofen, ifosfamide, tiagabine, ceftazidime, cefepime, and piperacillin-tazobactam, as well as neuroleptic malignant and serotonin syndromes (Wengs *et al*., 1993; Zak *et al*., 1994; Klion *et al*., 1994; Dike, 1997; Yoshino and Yoshimasu, 2000; Koepp *et al*., 2005; Fernández-Torre *et al*., 2005; Kaplan and Birbeck, 2006; Fernández-Torre *et al*., 2010). Of note, bursts of triphasic waves may not be recognised if quantitative EEG is used alone. Although the episode of MSE was controlled during anaesthesia with midazolam and the EEG showed a significant improvement, the presence of findings compatible with moderate encephalopathy was possibly due to multi-organ deterioration.

It is clear in our case that v-EEG was essential to reach diagnosis. Surface EEG helps to distinguish between cortical myoclonus, which responds to anticonvulsants such as levetiracetam, clonazepam, and valproate, and subcortical myoclonus, which may be of brainstem or spinal origin. Even trained and senior intensivists may have doubts about the nature of motor manifestations in severely ill comatose patients. Indeed, in a retrospective study, it was reported that non-epileptic events such as tremor-like movements, multifocal myoclonic jerks without electrographic changes, and slow semi-purposeful movements of the limbs or trunk, frequently mimic seizures in the ICU setting, and only bedside v-EEG recordings may help in the differential diagnosis (Benbadis *et al*., 2010). Interestingly, similar movements to those described by Hocker and Rabinstein (2011) (*e.g.* sudden and forceful opening and closing of the jaw) mimicking post-anoxic coma may also be observed in the video reported here. However, in the case report described by these authors, the surface EEG failed to show epileptiform discharges.

We are aware that CEEG is the method of choice for the evaluation of electrical brain activity in comatose patients. Full video-EEG has been adopted in most large medical centres because it has significant advantages (Fernández-Torre and Hernández-Hernández, 2012). We would like to highlight that under certain circumstances the bilateral BIS-VistaTM monitor may be helpful in the assessment of sedated patients with possible non-convulsive seizures or NCSE. This method has not been officially approved for continuous brain monitoring and its limitations should be taken into account, *i.e.* limited brain coverage, small number of EEG channels, and the need for careful interpretation in the presence of abundant muscle artefact and movement. Clearly, CEEG remains the gold standard for cerebral monitoring in the ICU, however, it is still not widely available. In the meantime, the use of alternative devices such as bilateral BIS may be helpful in monitoring selected cases of comatose NCSE.

Tacrolimus is an immunosuppressant drug that belongs to the group of calcineurin inhibitors, which has proven to be highly effective in preventing acute rejection after transplantation of solid organs. However, neurotoxicity and nephrotoxicity

are some of the most debilitating adverse effects associated with tacrolimus due to its impact on mental status and cognition (DiMartini *et al*., 2008). Patients typically present with cognitive impairment, delirium, coma, seizures, and posterior reversible encephalopathy syndrome. It appears that elderly patients, those with more advanced illness and worse post-liver transplant hepatic function, are at risk of developing tacrolimus-induced neurotoxicity (DiMartini *et al*., 2008). Severe neurotoxicity may occur even at therapeutic levels, and was initially considered as a cause of the comatose state and MSE in our patient. Myoclonic jerks have rarely been described in subjects receiving treatment with tacrolimus, although definitive interpretation of their origin remains elusive (Korzets *et al*., 2003). However, given the lack of clinical improvement following interruption of tacrolimus treatment, the clear temporal relationship between the onset of treatment with cefepime and occurrence of clinical manifestations, and the resolution of MSE after cefepime withdrawal, it is reasonable to rule out tacrolimus toxicity as a cause of neurological disorder exhibited by our patient.

Conclusion

In conclusion, cefepime may be a cause of MSE in non-anoxic comatose patients. Clinicians should be aware of this possibility when evaluating comatose patients on cephalosporin therapy in order to establish a correct diagnostic approach and accurate prognosis. □

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None of the authors have any conflict of interest to disclose.

Legends for video sequences

The spontaneous, irregular, and multifocal myoclonic jerks involving the face, limbs and trunk may be observed. These motor manifestations were predominant features in the clinical picture exhibited by the patient.

Key words for video research on www.epilepticdisorders.com

Syndrome: not applicable
Etiology: AED aggravation
Phenomenology: myoclonic seizure
Localization: not applicable

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