Epileptic Disord 2018; 20 (1): 73-6

De novo absence status epilepticus of late onset (DNASLO) precipitated by oral treatment with cefuroxime: description of an ambulatory case

José L Fernández-Torre [1,2,3], Alicia Paramio-Paz [1], Anjana López-Delgado [1], María Martín-García [1], Isabel González-Aramburu [3,4], Miguel A Hernández-Hernández [3,5]

[1] Department of Clinical Neurophysiology, Marqués de Valdecilla University Hospital, Santander, Cantabria
[2] Department of Physiology and Pharmacology, University of Cantabria (UNICAN), Santander, Cantabria
[3] Biomedical Research Institute (IDIVAL), Santander
[4] Department of Neurology, Marqués de Valdecilla University Hospital, Santander, Cantabria
[5] Department of Intensive Medicine, Marqués de Valdecilla University Hospital, Santander, Cantabria, Spain

Received February 25, 2017; Accepted July 31, 2017

ABSTRACT – We describe the case of an elderly woman with an episode of ambulatory *de novo* absence status epilepticus of late onset (DNASLO) after oral treatment with cefuroxime. A high level of suspicion of DNASLO in cases of unexplained confusion in adults or elderly subjects taking cephalosporins is essential to prompt an emergency EEG and, in turn, rapidly achieve an appropriate diagnosis and enable optimal treatment.

Key words: cefuroxime, non-convulsive status epilepticus, *de novo* absence status epilepticus, emergency EEG

During the past 15 years, clinical research has been directed to potential neurotoxic effects of intravenous cephalosporins (Martínez-Rodríguez *et al*., 2001; Fernández-Torre *et al*., 2005; Bora *et al*., 2016). Cefepime, ceftriaxone, and cefazolin are recognized causes of confusional episodes with generalized epileptiform activity on the EEG, representing an epileptic condition called "*de novo* absence status epilepticus of late onset" (DNASLO) (Thomas *et al*., 1992). This neurological complication occurs mainly in severely ill patients, often with renal failure and sepsis, in whom the use of high doses of intravenous antibiotics is required. In theory, cephalosporins can precipitate DNASLO since these antibiotics, by crossing the blood-brain barrier and binding competitively to gamma-aminobutyric acid (GABA; a major

Correspondence:
José L. Fernández-Torre
Department of Clinical Neurophysiology,
Marqués de Valdecilla University Hospital,
Avda. Valdecilla, 25,
39008 Santander,
Cantabria, Spain
<jlfernandez@humv.es>
<ftorrenfc@hotmail.com>

doi:10.1684/epd.2017.0938

inhibitory neurotransmitter in the brain) receptors, may lead to an imbalance between neuronal excitation and inhibition.
Herein, we describe the case of an elderly woman with ambulatory DNASLO after oral treatment with cefuroxime.

Case study

An independent 79-year-old woman was admitted to our hospital after 48 hours of behavioural abnormalities and disorientation. She had a history of hypertension and recurrent urinary tract infections, but no past history of epilepsy. She had undergone partial colectomy with adjuvant chemotherapy for colon adenocarcinoma three years previously. At the last visit, the oncologist considered her to be in complete remission. She was on chronic treatment with omeprazole, tolterodine tartrate, telmisartan, torasemide, calcifediol, and oral iron. She had started cefuroxime for acute media otitis the week before.
On neurological examination, she was confused and disoriented to time, with poor spontaneous speech and a mild tremor in both upper limbs. No focal motor or sensory deficits were seen. Routine laboratory tests, including renal parameters and computed tomography (CT) of the brain, were normal. An urgent video-electroencephalograhy (v-EEG) revealed frequent and recurrent generalized paroxysms of spike-wave complexes, intermixed with brief periods of normal background activity, in keeping with the diagnosis of DNASLO (*figure 1A, B*). Cefuroxime was discontinued, and intravenous treatment with levetiracetam (1,000 mg/day) was initiated. Twenty-four hours later, the patient returned to normal, with a normal follow-up EEG (*figure 1C*).

Discussion

DNASLO is a subtype of generalized non-convulsive status epilepticus (NCSE) that generally occurs in non-epileptic adults and elderly subjects, and is precipitated by drugs, toxins, metabolic disturbances or electroconvulsive therapy (Fernández-Torre *et al.,* 2015). Diverse pharmacological agents such as psychotropic medications, antidepressants, antiepileptic drugs, antibiotics, and antineoplastic agents have been reported as frequent causes of DNASLO. In clinical practice, we can distinguish two major subtypes of DNASLO:
– DNASLO precipitated by withdrawal of psychotropic drugs in elderly people;
– and DNASLO induced *by non-psychotropic drugs and other clinical situations* such as electroconvulsive therapy, metrizamide myelography or metabolic disturbances (Thomas *et al.,* 1992; Thomas and Andermann, 1994; Fernández-Torre *et al.,* 2012; Fernández-Torre *et al.,* 2015).
Thus, patients with DNASLO *induced by non-psychotropic drugs* frequently have moderate or severe concomitant disorders including sepsis or serious infections, renal failure, cancer, or metabolic derangements. Therefore, the episodes of DNASLO induced by non-psychotropic drugs occur in different clinical contexts compared to those described in patients on chronic psychotropic medications. Many of these non-psychotropic drugs are associated with episodes of absence status epilepticus (ASE) that occur in children, adolescents or young adults, hence not "of late onset".
The condition described here was not treated with intravenous benzodiazepines (IVBZDs). The administration of IVBZDs is considered key in making a "definitive" diagnosis of NCSE (Kaplan, 1999), and is routine practice in our department (Fernández-Torre *et al*., 2012). However, in this case, IVBZDs were not administrated because of clinical and physiological considerations. The resolution of the clinical and EEG anomalies after treatment with short-acting antiepileptic drugs is diagnostic of NCSE (Kaplan, 2005). A recent study concluded that a clinical response to acute IVBZDs in patients with NCSE is predictive of survival and better functional recovery (Hopp *et al*., 2011). However, it is well-known that the administration of IVBZDs for confirming the diagnosis of NCSE may have limitations in clinical practice:
– both triphasic waves and periodic sharp-wave complexes of toxic-metabolic or degenerative origin and generalized epileptiform discharges may regress with IVBZDs;
– an immediate clinical improvement can be difficult to evaluate in patients under the hypnotic effects of IVBZDs (the patients frequently fall into deep sleep);
– and the absence of a clinical improvement is not always a definite sign of regression of NCSE, as there may be a delay in clinical improvement in NCSE.
It is important to exclude an idiopathic generalized epilepsy (IGE), even when the patient is elderly. Older individuals with a history of IGE may also present with ASE, sometimes under circumstances that initially appear similar to those that can trigger *de novo* episodes (Koutroumanidis, 2009; Fernández-Torre *et al.,* 2012). Moreover, several investigators have emphasized that ASE in elderly individuals is not always a situation-related condition and may occur as a delayed complication of IGE (Zambrelli *et al.,* 2006; Bauer *et al.,* 2007; Fernández-Torre and Rebollo, 2009; Fernández-Torre *et al.,* 2012). Zambrelli *et al*. (2006) reported an octogenarian woman with recurrent episodes of ASE and clinical and EEG features consistent with IGE. Recently, Bauer *et al*. (2007) described four similar elderly women, all of whom had a history consistent

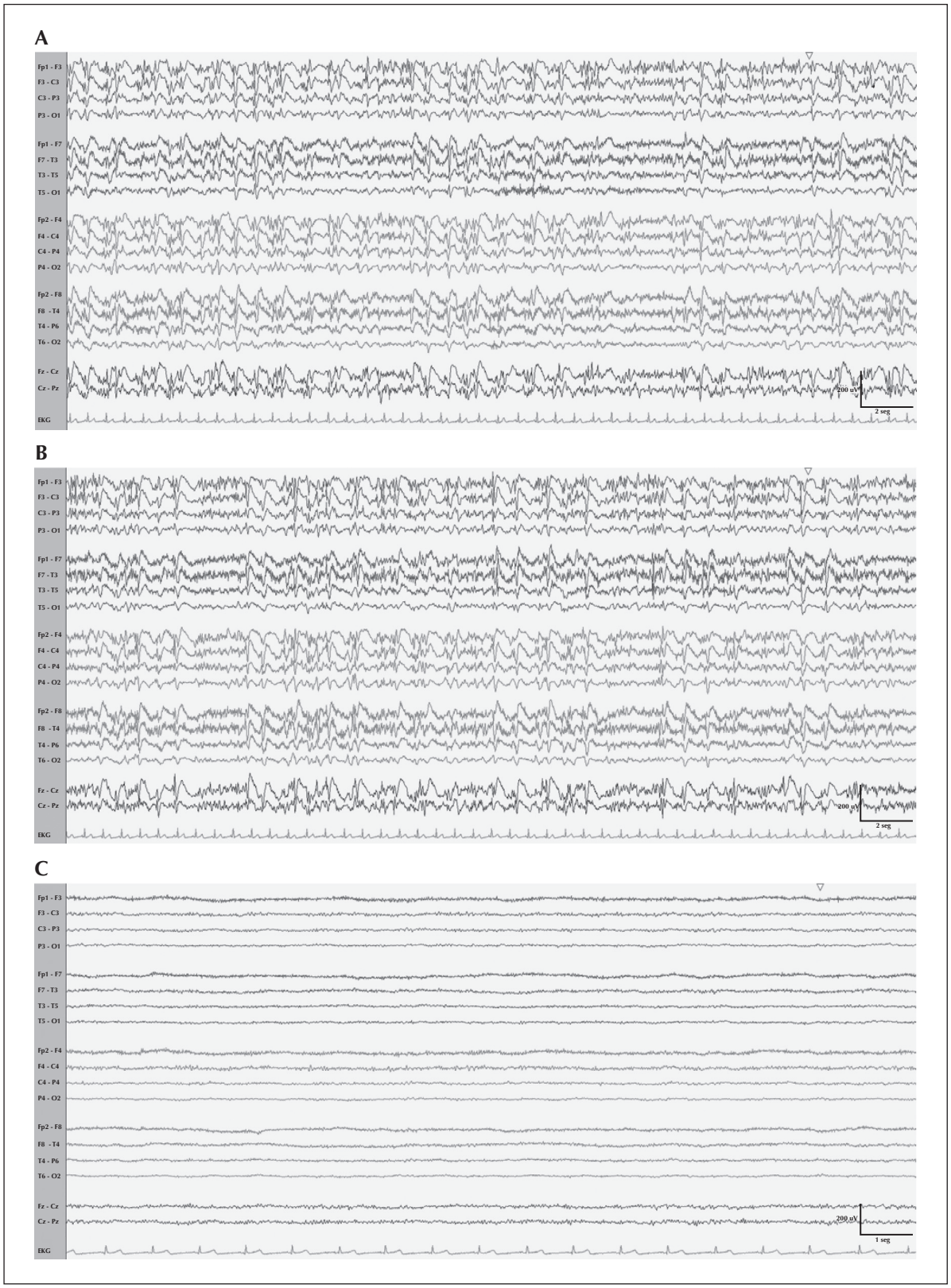

Figure 1. (A, B) The presence of recurrent generalized paroxysms of spike-wave complexes, compatible with a diagnosis of DNASLO. (C) Low-voltage EEG following the onset of antiepileptic therapy. Double banana montage; low filter: 0.53 Hz; high filter: 70 Hz; notch filter: 50 Hz; vertical bar: 200 μV; horizontal bar: 2 seconds (A, B) and one second (C).

with pre-existing IGE, with absence seizures and repeated episodes of ASE after the age of 60 years. The authors emphasised that the diagnosis of IGE remains a possibility in older subjects with DNASLO. Interestingly, in our case, the use of oral treatment with cefuroxime was the precipitating factor of DNASLO, rarely seen in daily clinical practice. Taking into account that DNASLO is a condition linking confusion and epileptiform discharges on the EEG, the elimination of the offending factor might be curative. However, it is likely that both the use of antiepileptic drugs and the interruption of cephalosporin therapy led to faster clinical improvement, and arguably reduced complications and the potential for brain damage (Fernández-Torre *et al*., 2005).

Cephalosporins, such as cefepime, ceftazidime, and ceftriaxone, may be associated with confusional episodes with generalized epileptiform activity on the EEG, as observed in non-comatose and comatose patients (Fernández-Torre *et al*., 2005; Naeije *et al*., 2011; Fugate *et al*., 2013). This neurological complication occurs generally in subjects with impaired renal function in whom the cephalosporin dosages have not been adequately adjusted to the patient's impaired renal clearance. However, episodes of DNASLO in association with oral cefuroxime treatment have not been previously reported. Interestingly, renal function in our patient was normal. Herishanu *et al*. (1998) described four patients with cefuroxime-induced encephalopathy. The clinical picture was acute and reversible, and obtundation or stupor and myoclonic jerks were predominant symptoms. In all of their patients, the EEG showed generalized slowing, but epileptiform activity was completely absent. Of note, the differential diagnosis of a confused patient under cefepime therapy also includes encephalopathy per se, *i.e*. with slowing of the background activity or triphasic waves, but without epileptiform activity; this is also a good reason to perform an urgent EEG.

In summary, we would like to highlight that oral treatment with cefuroxime may induce an episode of DNASLO. A high level of suspicion of DNASLO in cases of unexplained confusion in adults or elderly subjects taking cephalosporins is essential in order to lead to an emergency EEG, which may enable prompt diagnosis and appropriate and optimal treatment. □

Disclosures.

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

References

Bauer G, Bauer R, Dobesberger J, Benke T, Walser G, Trinka E. Absence status in the elderly as a late complication of idiopathic generalized epilepsy. *Epileptic Disord* 2007; 9: 39-42.

Bora I, Demir AB, Uzun P. Nonconvulsive status epilepticus cases arising in connection with cephalosporins. *Epilepsy Behav Case Rep* 2016; 6: 23-7.

Fernández-Torre JL, Rebollo M. Typical absence status epilepticus as late presentation of idiopathic generalised epilepsy in an elderly patient. *Seizure* 2009; 18: 82-3.

Fernández-Torre JL, Martínez-Martínez M, González-Rato J, *et al*. Cephalosporin-induced nonconvulsive status epilepticus: clinical and electroencephalographic features. *Epilepsia* 2005; 46: 1550-2.

Fernández-Torre JL, Rebollo M, Gutiérrez A, Gutiérrez A, López-Espadas F, Hernández-Hernández MA. Nonconvulsive status epilepticus in adults: electroclinical differences between proper and comatose forms. *Clin Neurophysiol* 2012; 123: 244-51.

Fernández-Torre JL, Kaplan PW, Hernández-Hernández MA. New understanding of nonconvulsive status epilepticus in adults: treatments and challenges. *Expert Rev Neurother* 2015; 15: 1455-73.

Fugate JE, Kalimulah EA, Hocker SE, Clark SL, Wijdicks EFM, Rabinstein AA. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. *Critical Care* 2013; 17: R264.

Herishanu YO, Zlotnik M, Mostoslavsky M, Podgaietski M, Frisher S, Wirguin I. Cefuroxime-induced encephalopathy. *Neurology* 1998; 50: 1873-5.

Hopp JL, Sanchez A, Krumholz A, Hart G, Barry E. Nonconvulsive status epilepticus. Value of a benzodiazepine trial for predicting outcomes. *The Neurologist* 2011; 17: 325-9.

Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol* 1999; 16: 341-52.

Kaplan PW. The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus. *The Neurologist* 2005; 11: 348-61.

Koutroumanidis M. Absence status epilepticus. In: Kaplan PW, Drislane FW, eds. *Nonconvulsive Status Epilepticus*. New York: Demos Medical Publishing, 2009, 145-166.

Martínez-Rodríguez JE, Barriga FJ, Santamaría J, *et al*. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. *Am J Med* 2001; 111: 115-9.

Naeije G, Lorent S, Viecent JL, Legros B. Continuous epileptiform discharges in patients treated with cefepime or meropenem. *Arch Neurol* 2011; 68: 1301-5.

Thomas P, Andermann F. Late-onset absence status epilepticus is most often situation-related. In: Malafosse A, Genton P, Hirsch E, Marescaux C, Broglin D, Bernasconi R, eds. *Idiopathic Generalized Epilepsies*. London: John Libbey & Company Ltd, 1994, 95-109.

Thomas P, Beaumanoir A, Genton P, Dolisi C, Chatel M. 'De novo' absence status of late onset: Report of 11 cases. *Neurology* 1992; 42: 104-10.

Zambrelli E, Terzaghi M, Sinforiani E, Manni R. Nonconvulsive status epilepticus and generalised tonic-clonic seizures persisting in old age in a patient with idiopathic generalised epilepsy: a long-observation. *Neurol Sci* 2006; 27: 436-8.