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Case report

Myoclonus induced by amoxicillin-clavulanic acid

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1. Introduction

The adverse neurological effects of antibiotics are well known, although not common, with an estimated incidence of less than 1% [1]. Among these adverse effects, seizures and movement disorders are observed in different families of antibiotics: beta-lactams (seizure, myoclonus, status epilepticus, tremor, asterixis), quinolones (seizure, status epilepticus, dyskinesias, choreiform movements), sulfonamides, antimalarials and ivermectin (tremor, seizure), oxazolidinones, polymyxins and nitroimidazoles (seizure), lipoglycopeptides (tremor), antifungals (myoclonus) and antivirals (tremor, myoclonus) [1–3]. Regarding beta-lactams, specifically penicillins, their proconvulsive potential has been observed and verified for decades in different animal and human models after direct application to the cerebral cortex [4]. Myoclonus is a well-known manifestation of epilepsy, observed mainly within the group of generalized idiopathic epilepsies. It has also been described as secondary to different antibiotics [1,5]. Among penicillins, to our knowledge, there is a single reported case that relates myoclonus to treatment with amoxicillin [6]. In the current case, a 64-year-old patient presented with generalized myoclonus associated with the initiation of treatment with amoxicillin for acute sinus infection. No anatomic changes on neuroimaging were observed. However, electroencephalography (EEG) revealed intermittent bursts of polyspikes with high amplitudes in the fronto-central regions. After discontinuing antibiotic treatment, both myoclonus and EEG changes disappeared. Herein, we describe the case of a patient with myoclonus secondary to antibiotic treatment with amoxicillin-clavulanic acid.

2. Clinical case

A 92-year-old patient presented with a history of arterial hypertension, type 2 diabetes, heart failure, benign prostatic hypertrophy (permanent bladder catheter user), stage 4 chronic kidney disease (typical creatinine values ~2–2.50 mg/dl and CKD-EPI glomerular filtration rate of 23 ml/min/1.73 m^2), and uninvestigated moderate cognitive impairment of probable neurodegenerative origin. The patient was under routine treatment with ranitidine 150 mg every 24 h, valsartan 160 mg every 24 h, amlodipine 10 mg every 24 h, hydrochlorothiazide 25 mg every 24 h, vildagliptin 50 mg every 24 h, metformin 850 mg every 24 h and acetylsalicylic acid 100 mg every 24 h. He was admitted to the hospital due to fever without evident source, initially managed as a urinary tract infection; therefore, antibiotic treatment with ceftazidime was initiated. Apart from this treatment, the patient was administered 20 mg omeprazole every 24 h and 1 g paracetamol every 8 h, in addition to the usual medication. Twenty-four hours after admission, he presented with dental phlegmon; treatment with ceftazidime was suspended, and treatment with intravenous amoxicillin-clavulanic acid was initiated at a dose adjusted to renal function (500 mg every 12 h). After receiving the second dose of treatment, the patient began showing a pattern of sudden, irregular, lightening-like fast jerks, at varying intervals of less than 1 min, in the perioral region and in the upper extremities, compatible with myoclonus, during which time the patient maintained alertness and no other neurological signs or symptoms were observed. At that time, no significant changes in complete blood count or biochemistry parameters, except for a creatinine level of 2.32 mg/dl and glomerular filtration rate of 23.5 ml/min/1.73 m^2, which were at baseline for the patient. Brain CT showed diffuse cerebral atrophy without evidence of acute alterations (Fig. 1). EEG showed frequent bursts of acute rhythmic discharges with bilateral fronto-central distribution (Fig. 2), with many of them correlated with myoclonic jerks. Given the clinical picture, a single dose of levetiracetam 500 mg was administered, with partial improvement, observing myoclonus of milder intensity and lower frequency, although continued. It was decided to discontinue treatment with amoxicillin-clavulanic acid after it was suspected to be the origin of the myoclonus, replacing it with 300 mg oral clindamycin every 8 h. After this modification, the patient was asymptomatic, and a repeat EEG was performed at 24 h, which showed no acute graphoelements. Once discharged from the hospital after receiving treatment for his infectious pathology, the patient has not presented new episodes of myoclonus.

3. Discussion

Antibiotics, including beta-lactams, are drugs for which the onset of seizures is a known side effect [5,7]. Different groups of beta-lactams, such as cephalosporins, carbapenems and penicillins, are typically associated with this adverse event. Myoclonus has been described in

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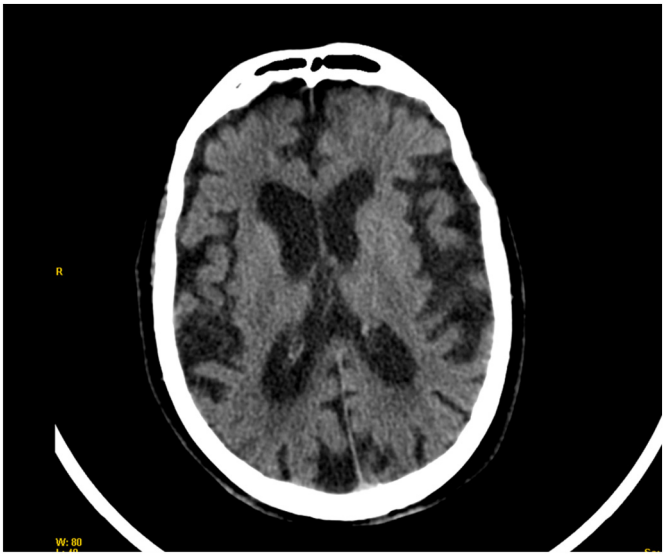

Fig. 1. Brain CT scan: diffuse moderate to severe cortico-subcortical brain atrophy is observed, without evidence of acute processes, space-occupying lesions or other alterations.

epileptic seizures induced by beta-lactams [7]. Its pathophysiology is probably related to the inhibition of cortical GABAergic neurotransmission of structural cause due to the beta-lactam ring, which has certain molecular similarities with these neurotransmitters and binds to the $GABA_A$ receptor, leading to a decrease in inhibitory postsynaptic potentials and thus to an increase in neuronal excitability [5,7,8]. However, among penicillins, there is a relative lack of reports on the association of amoxicillin-clavulanic acid with seizures, despite its broad-spectrum profile and widespread use, especially in countries where an intravenous formulation is available. This may be due to its poor entry into the central nervous system through the blood–brain barrier, or limited similarity to hydroxypenicillins, and pharmacokinetic and pharmacodynamic properties that limit binding to the $GABA_A$ receptor binding site suitable for more lipophilic penicillins [7]. In contrast, it has been observed in animal models that clavulanic acid does not affect the convulsive threshold, and potential neuroprotective and antiepileptic properties have been suggested [9]. This is consistent with the lack of reports associating amoxicillin-clavulanic acid with seizures and myoclonus, and suggests that amoxicillin is the main component responsible for these adverse effects and typically, amoxicillin-clavulanic acid is a penicillin with low epileptogenic risk.

Clinically, myoclonus secondary to antibiotics has been described as either generalized, multifocal or subtle, affecting small muscle groups [5] (periocular or perioral, as in our case). In many cases, it is associated with a low level of alertness, encephalopathy or delirium [5,8]. There are certain clinical factors that facilitate the onset of myoclonus in this antibiotic pharmacological context: advanced age, high or toxic antibiotic doses, renal insufficiency and the presence of an underlying brain disease [3,5,6]. In our case, 3 of these factors were observed: a very old patient, chronic kidney disease and an underlying case of neurodegenerative cognitive impairment. This last factor was not a previously identified diagnosis but was clinically compatible according to the interview conducted with the patient's relatives and to certain findings in complementary explorations (brain atrophy on neuroimaging and the presence of diffuse slowing of background activity on EEG [10], without clinical

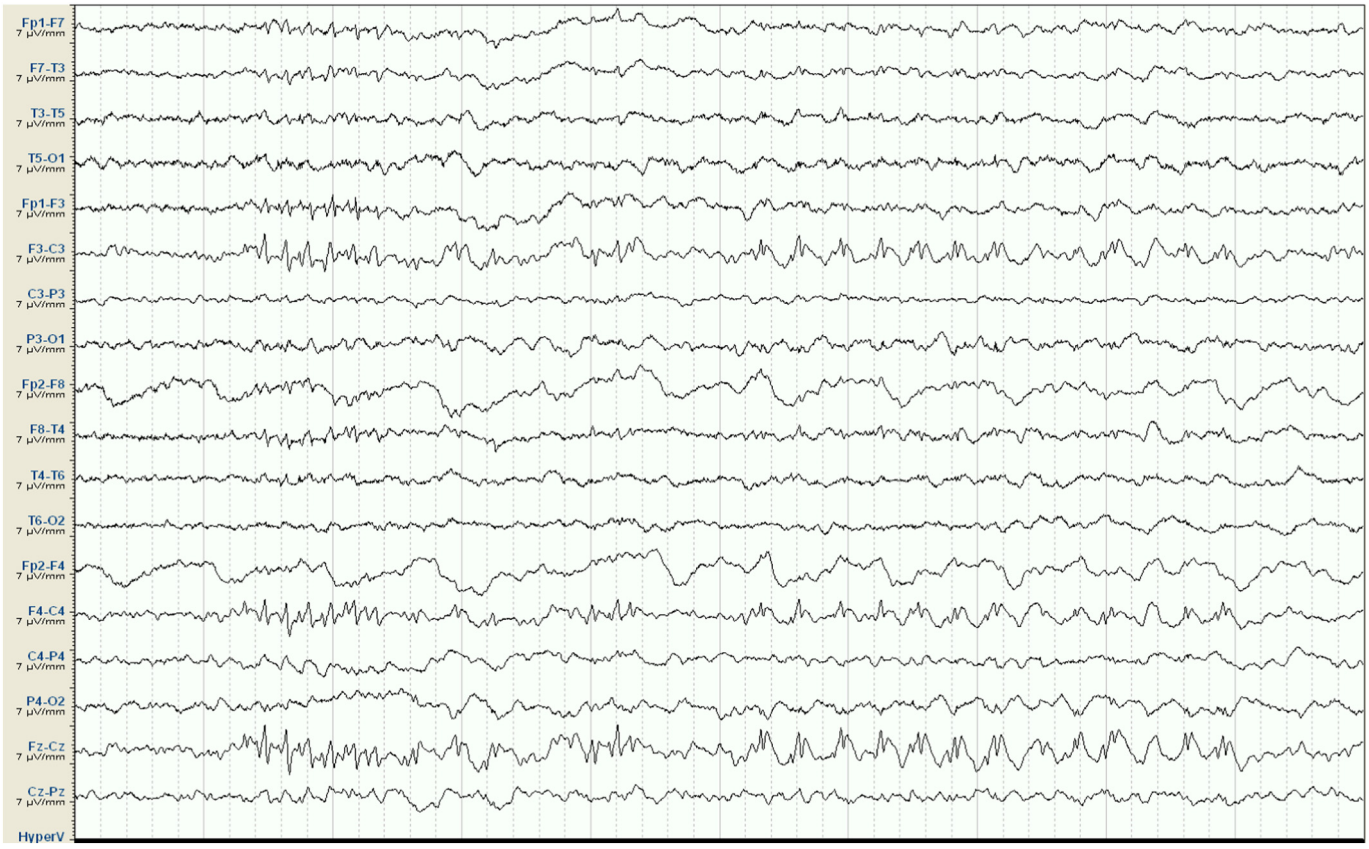

Fig. 2. Electroencephalogram (EEG) during repeated myoclonus. Background rhythm was slightly slowed, showing a sharp rhythmic discharge predominantly in bilateral fronto-central areas, followed by an outburst with a rhythmic delta activity pattern with overlapping polyspikes.

signs of encephalopathy), suggesting Alzheimer's disease. Most likely, factors specific to the patient (i.e., age, renal clearance) were very important for the development of myoclonus. Therefore, these factors should be considered to identifying patients at greater risk of developing side-effects in routine clinical practice.

In our opinion, this case had a clear temporal correlation between the initiation of antibiotic treatment and the onset of persistent myoclonus. No other evidence of associated metabolic, central nervous system or systemic alterations were detected. In addition, myoclonus was limited after suspending treatment with amoxicillin-clavulanic acid. Furthermore, clear improvement in the EEG was also observed to support this association. It is true that there is a possible confounding factor, such as treatment with levetiracetam. However, this treatment involved a single dose that reduced but did not eliminate myoclonus. Also, resolution of myoclonus occurred gradually overtime following the last dose of amoxicillin-clavulanic acid. To our knowledge, our case is the first reported in which the onset of myoclonus secondary to treatment with amoxicillin-clavulanic acid is observed; thus far, with only one case associated with amoxicillin previously reported [6]. Despite being a rare adverse effect, we believe it is important for clinicians to understand so that it can be quickly detected and appropriate steps can be initiated. First, immediately stop treatment with amoxicillin-clavulanic acid and substitute treatment with another antibiotic with a lower proconvulsive potential based on the patient's infectious etiology. Next, assess the need for antiseizure medication until resolution of the condition taking into account the intensity and clinical impact of myoclonus along side the risk–benefit balance of treatment. We believe these premises can be useful to address this unusual complication, avoiding unnecessary aggressive therapeutic maneuvers.

Ethical statement

The authors ensure that this work has been carried out in accordance with the Declaration of Helsinki.

Declaration of competing interest

The study was not funded by any public or private entity. The authors declare no conflicts of interest.

References

[1] Bangert MK, Hasbun R. Neurological and psychiatric adverse effects of antimicrobials. CNS Drugs. 2019;33(8):727–53.
[2] Dawson ET, Hocker SE. Neurologic complications of commonly used drugs in the hospital setting. Curr Neurol Neurosci Rep. 2016;16(4):35.
[3] Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol. 2011;72(3):381–93.
[4] Walker AE, Johnson HC, Kollros II. Penicillin convulsions; the convulsive effects of penicillin applied to the cerebral cortex of monkey and man. Surg Gynecol Obstret. 1945;81:692–701.
[5] Janssen S, Bloem BR, van de Warrenburg BP. The clinical heterogeneity of drug-induced myoclonus: an illustrated review. J Neurol. 2017;264:1559–66.
[6] Raposo J, Teotónio R, Conceiçao B, Sales F. Amoxicillin, a potential epileptogenic drug. Epileptic Disord. 2016;18(4):454–7.
[7] Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs. Neurology. 2015;85:1332–41.
[8] Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL. Antibiotic-associated encephalopathy. Neurology. 2016;86(10):963–71.
[9] Gasior M, Socala K, Nieoczym D, Wlaz P. Clavulanic acid does not affect convulsions in acute seizure tests in mice. J Neural Transm (Vienna). 2012;119(1):1–6.
[10] Horvath A, Szucs A, Csukly G, Sakovics A, Stefanics G, Kamondi A. EEG and ERP biomarkers of Alzheimer's disease: a critical review. Front Biosci (Landmark Ed). 2018;23:183–220.