Clinical commentary

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Amoxicillin, a potential epileptogenic drug*

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ABSTRACT – Beta-lactams are known to cause a wide spectrum of neurotoxic manifestations including epileptic seizures. The neurotoxicity of penicillin was first reported in 1945 by Johnson and Walker and is believed to exert an inhibitory effect on gamma-aminobutyric acid transmission of cortical pyramidal cells, due to its beta-lactam ring structure. Epileptogenicity is also a feature of the semisynthetic beta-lactams including aminopenicillins. In this report, we present a patient with a recurrent history of discrete body twitching/jerks of epileptic nature in the context of amoxicillin exposure. The EEG revealed intermittent generalized short bursts of beta-frequency polyspikes. This electro-clinical picture was reversed by amoxicillin discontinuation.

Key words: amoxicillin, beta-lactam, epileptogenic drug

Central nervous system toxicity caused by drug exposure is a common reason for presentation to the emergency department. Antibiotics are among the most frequently used drugs in both the inpatient and outpatient setting. Beta-lactams are known to cause a wide spectrum of neurotoxic manifestations including encephalopathy, behavioural changes, myoclonus, seizures, as well as non-convulsive status epilepticus (Hantson *et al*., 1999; Chow *et al*., 2005). The neurotoxicity of penicillin was first reported in 1945 by Johnson and Walker, who observed myoclonic twitching after intravenous administration (Johnson and Walker, 1945). The epileptogenic and antimicrobial properties of beta-lactams are structure-dependent and the beta-lactam ring is a key feature of penicillin epileptogenesis; these properties are abolished if the beta-lactam ring is enzymatically cleaved. Beta-lactams are believed to exert an inhibitory effect on gamma-aminobutyric acid transmission of cortical pyramidal cells due to their beta-lactam ring structure, which shares similar molecular architecture to that of GABA neurotransmitters. Benzylpenicillin appears to have the most epileptogenic potential among all beta-lactams, but epileptogenicity is also a feature of the semisynthetic beta-lactams, including aminopenicillins (amoxicillin, ampicillin, *etc*.) and carbapenems

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(Miller *et al*., 2011). Meropol and co-authors identified a seizure incidence rate, per 1,000,000 person-days of exposure, of 2.6-4.8 for patients with short-term exposure to amoxicillin (Meropol *et al*., 2008). Drug-induced seizures cover seizures precipitated by drugs in susceptible non-epileptic patients and seizures that may occur in epileptic patients after withdrawal of pharmacotherapy or triggered by a pro-epileptic drug. In many cases, there are some predisposing factors, such as renal failure or blood-brain barrier disruption (*e.g.* meningitis or underlying brain disease) (Norrby, 2000; Chow *et al*., 2004). Every human being can have a seizure under certain circumstances and about 10% of the population has a low seizure threshold that may allow seizures to be triggered by a wide range of stimuli, such as fever in infancy, drugs, and biochemical disturbances (Brodie and Schachter, 1999). Drug-induced seizures are usually self-limiting and do not recur if the offending drug is discontinued, except when brain damage caused by a drug acts as an epileptic focus.

Clinical study

A 64-year-old man presented to an emergency department with a history of discrete jerks affecting the entire body (muscle twitching) over a period of a few days, without perturbation of consciousness and no other complaints. Shortly before the onset of body twitching, he was treated with amoxicillin in the setting of exacerbation of sinusopathy. The patient reported an identical episode about six months before, during the same setting of amoxicillin treatment, with spontaneous remission at the end of the treatment. He had no known history of epilepsy or epileptic seizures and he reported no other relevant clinical history. The patient was pre-medicated only with omeprazol. On examination, he had intermittent bursts of fast subtle clonic twitching, apparently involving the entire body with no other apparent clinical manifestations or subjective complaints. On admission, neuroimaging (brain CT) evaluation was normal, except for signs of inflammatory polypoid pansinusitis. The patient did not complain of fever, headache, vomiting, or meningism. Full ionogram (Na+, K+, Cl-, Ca2+ and Mg2+), ALT, AST, GGT, prothrombin time, and creatinine and urea levels were within normal range. There was no concomitant metabolic derangement, nor liver or kidney failure, and we did not find any sign of secondary intracranial infection or neurodegenerative disorder. He had undergone a video-EEG that revealed intermittent generalized short bursts (lasting for one to three seconds) of beta-frequency polyspikes (13-14 Hz) with higher amplitude in the fronto-central regions (F4-C4, F3-C3, Fz-Cz). The spike bursts were time-locked to the fast multifocal clonic twitching and were registered with a few frontal intermittent rhythmic delta activity (FIRDA) bursts during wakefulness (*figures 1, 2*). The amoxicillin was changed to clarithromycin and both the clonic jerks and EEG anomalies disappeared. The patient was discharged from the hospital to home, and returned to normal life.

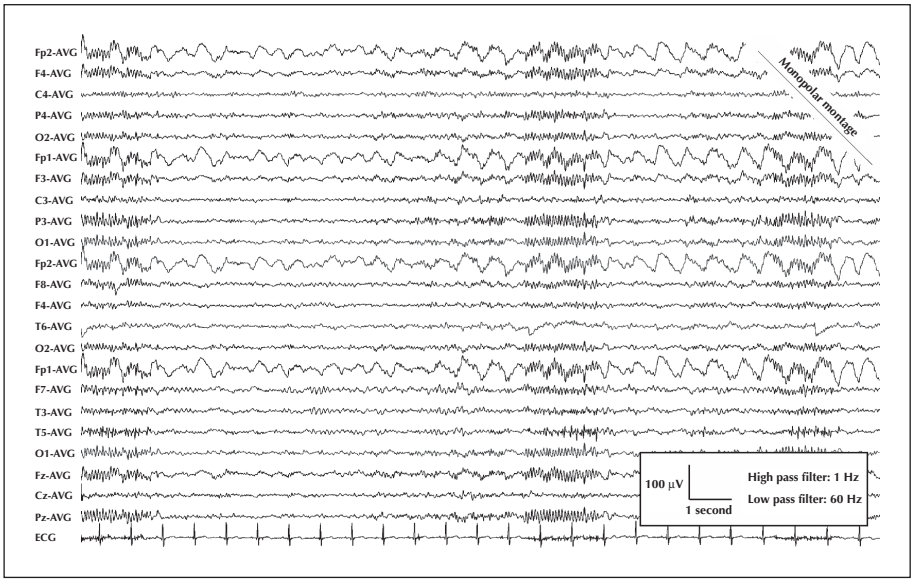

Figure 1. EEG on admission, performed using the 10-20 reference montage (average) and recorded during wakefulness, revealed intermittent short bursts (lasting for one to three seconds) of beta-frequency polyspikes (13-14-Hz), which were widespread in almost all channels with higher amplitude in the fronto-central regions (F4-C4, F3-C3, Fz-Cz). The spike bursts were time-locked to the multifocal clonic twitching (see muscle artefact on ECG channel). FIRDA bursts are not shown in this figure.

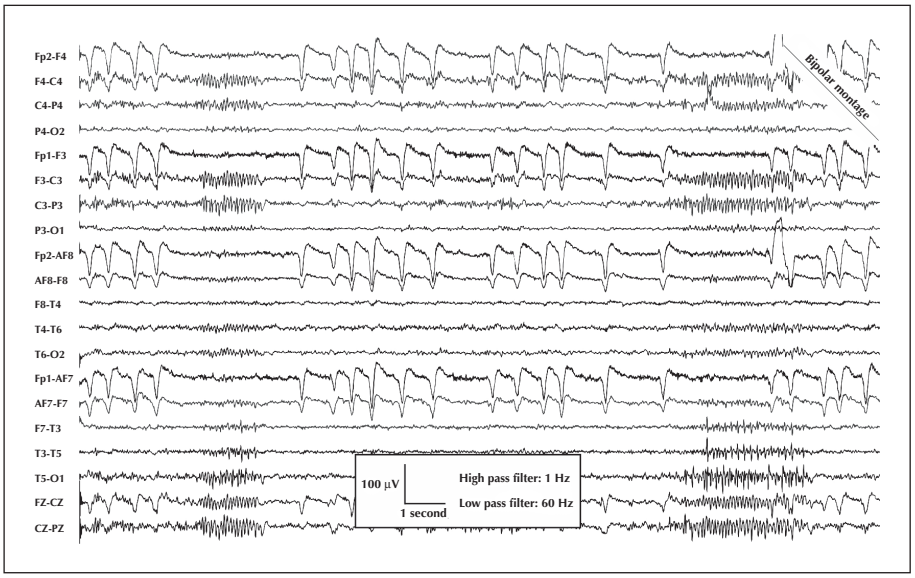

Figure 2. EEG on admission, performed using the 10-20 longitudinal bipolar montage (plus additional AF7/AF8) and recorded during wakefulness, showing the same pattern as described in *figure 1*.

Discussion

Beta-lactams are known to cause a wide range of epileptogenic manifestations in susceptible epileptic and non-epileptic patients. There is a need for drug-induced seizures to be categorized in the same way that other epileptic seizures have been categorized. Suspicion of association with a particular drug can be verified by discontinuation of the drug followed by improvement of seizures, and aggravation of seizures on reintroduction of the drug. In our case, amoxicillin exposure was associated with fast multifocal clonic jerks, time-locked to bursts of generalized beta-frequency polyspikes on EEG. For this non-epileptic patient, no known predisposing metabolic or constitutional factors, commonly described in the literature, were identified. To our knowledge, this is the first case report of amoxicillin and myoclonic seizures. However, as a single case report, no direct causality can be concluded. Drug-induced seizures are usually self-limiting and do not recur if the offending medication is discontinued, as was the case in our patient. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
The authors report no biomedical financial interests or potential conflicts of interest.

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TEST YOURSELF

(1) What kind of neurotoxic effects are known with respect to beta-lactams?

(2) By what mechanism does amoxicillin exhibit its epileptogenic effect?

(3) Why is it so important to keep in mind the epileptogenic potential of commonly used drugs?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".