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Case Report

Efficacy of perampanel in a patient with epilepsia partialis continua

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ABSTRACT

Perampanel is the first-in-class selective and noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist. It is authorized in the U.S. and Europe as an add-on antiepileptic drug for partial-onset seizures, and for primary generalized tonic–clonic seizures. Single reports have also indicated a potential efficacy for myoclonic jerks. Here, we report a patient whose drug-resistant epilepsia partialis continua completely resolved after adding perampanel. She has remained seizure-free in an eighteen-month follow-up period. Epilepsia partialis continua reemerged transiently after perampanel was temporarily discontinued, with no recurrence after its reintroduction. Therefore, this effect was reproducible, and suggests that it might be worth trying perampanel in similar settings.

1. Introduction

Perampanel (PER) is a third-generation antiepileptic drug (AED), first-in-class selective and noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. It has been approved and marketed as an add-on AED in partial-onset seizures with or without secondary generalization [1], and in primary generalized tonic–clonic seizures in patients from 12 years of age [2]. Large series in real life have proven the efficacy of PER in focal epilepsy [3,4]. Furthermore, single reports and short series have suggested a potential efficacy of PER in other specific conditions, such as myoclonic jerks in progressive myoclonic epilepsy like Lafora disease [5–7], and in Lance–Adams syndrome [8]. Although its efficacy and safety in the elderly have been previously highlighted [3,9], no clinical experience has been reported among this special population in epilepsia partialis continua (EPC).

2. Case report

Our patient is a 76-year-old woman whose past medical history is significant for hypertension and dyslipidemia. In 2014, she was diagnosed with a left frontal meningioma after having motor partial-onset seizures and paresis in her right upper limb along with mild motor aphasia. After surgical removal, she was prescribed and administered levetiracetam (LEV) at 1000 mg/day, and became seizure-free for one year. In September 2015, she was admitted to the Neurology ward due to continuous involuntary movements of her right arm lasting seven days. On exam, she had continuous clonic movements on her right hand, forearm and hemiface, along with right upper extremity paresis and motor aphasia. The remaining neurological exam was normal. Multichannel digital electroencephalogram (EEG) recordings using the international 10–20 placement system were obtained throughout the episode. Background rhythm during the awakened stage showed an average voltage of 8 to 9 hertz alpha activity in the posterior regions that blocked with eye opening. Beta activity was observed in anterior regions. No epileptiform discharges or focal abnormalities were seen. There was no modification during photic stimulation and hyperventilation. A brain magnetic resonance imaging (MRI) showed no changes from an identical screening a year prior (Fig. 1.). Not withstanding uneventful EEG recordings, based on clinical grounds, the diagnosis of EPC was established. Initially, she was treated with 1.5 mg/day of clonazepam (CZP), 1000 mg/day of LEV, and 400 mg/day of lacosamide (LCM). Seizures faded away, but she became significantly drowsy. Therefore, we decreased CZP, which subdued drowsiness, but seizures relapsed. Afterwards, we introduced PER progressively, 2 mg/day for two weeks and then 4 mg/day, as maintenance treatment in polytherapy with LEV and LCM. We observed substantial improvement on 2 mg, and seizure-freedom was achieved on 4 mg, with no side effects.

Six months later, the patient reported significant irritability. Given the lack of seizures, PER was slowly tapered until discontinuation. Immediately, EPC showed up again, so PER was reintroduced slowly throughout four weeks until the previous dose of 4 mg/day was

Abbreviations: PER, perampanel; AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EPC, epilepsia partialis continua; LEV, levetiracetam; EEG, electroencephalogram; MRI, magnetic resonance imaging; CZP, clonazepam; LCM, lacosamide; RCT, randomized clinical trials.

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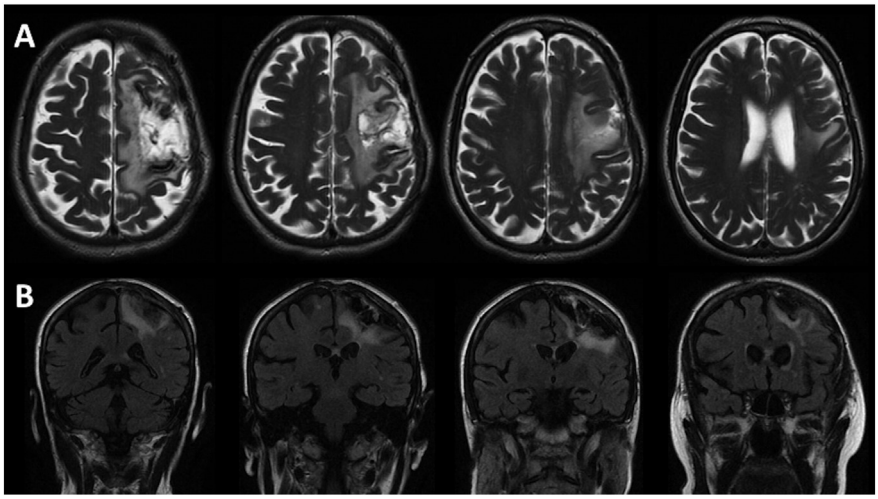

Fig. 1. (A) Axial T2- and (B) coronal FLAIR-weighted MRI sequences disclose the remnants of the meningioma in the left frontal and parietal lobe, affecting mainly the precentral gyrus.

reached. EPC was suppressed again. She has remained seizure-free and no side effects were reported in the last appointment, twelve months later.

3. Discussion

EPC is a rare and especially refractory focal motor status epilepticus. It consists of regular jerking activity, typically involving the hand and face. It can be very persistent, lasting as long as years [10]. EPC may complicate common cerebral lesions such as brain tumors [11,12], or infrequent disorders like Rasmussen encephalitis [13,14], apart from many other conditions [15]. In our patient, we hypothesize that the meningioma remnants along with surrounding cerebral edema contributed to the development of an epileptogenic network in the left frontal area over several months, which eventually caused her to experience this type of seizure. EPC may produce detectable focal discharges of cortical origin [10]. However, a normal scalp EEG does not refute the diagnosis of EPC, as ictal EEG can be uneventful in 18% of patients [16]. In general, patients with EPC are rather drug-resistant, with 30% suffering persistent EPC despite polytherapy [16]. Recently, isolated cases of patients with EPC have shown a positive response to add-on LCM [17], vagal nerve stimulator [18,19] or neocortical electrical stimulation [20]. Based on previously communicated efficacy of PER in focal epilepsy and in other less frequent conditions (such as myoclonic jerks in different epileptic disorders [5–8]), we tried PER in this patient with refractory EPC. We used PER in combination with LEV and LCM, which resulted in a sustained suppression of seizures in an eighteen-month follow-up, with limited and temporary side effects. A challenge–dechallenge–rechallenge design was applied to test the efficacy of PER. EPC was suppressed when PER was added the first time (challenge), it relapsed after stopping this AED (dechallenge) and seizure-freedom was achieved again when PER was reintroduced (rechallenge). This evolution suggests that PER, possibly through a synergism with the other AEDs, is playing a key role in controlling the seizures in this patient. In addition, this case also illustrates that rational polytherapy, using a combination of AEDs with different mechanisms of action, is a recommended way to manage patients with refractory epilepsy. PER-related irritability can be avoided with a slow titration [3,21]. In our patient, it was controlled with a slowly progressive introduction (in the second attempt). Another titration schedule could have been considered given the impairment condition (e.g. starting with 4 mg instead of 2 mg). We decided to initiate PER with 2 mg because AED clearance and metabolism are reduced in the elderly, making them more susceptible to side effects. In addition, the effective dose (4 mg/day) was lower than the one used in randomized clinical trials (RCT) [22]. This fact may be due to her advanced age and supports the usefulness of real-world data to clarify unresolved issues in RCT, like titration and dosage.

4. Conclusion

We found that PER-polypharmacy proved to be effective in the long-term for a patient with refractory EPC. In the light of this observation, we recommend the use of PER as an add-on AED for refractory cases of EPC, and we suggest that slow titration and low doses be considered in the elderly to achieve an adequate tolerability.

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