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Case Report

Perampanel: A therapeutic alternative in refractory status epilepticus associated with MELAS syndrome

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ABSTRACT

To our knowledge, there are no reports of status epilepticus (SE) associated with mitochondrial diseases and treated with perampanel (PER). We present three cases of patients with refractory SE associated with MELAS syndrome who responded favorably to PER.

All cases were diagnosed as non-convulsive SE (focal without impairment of level of consciousness). After an initial treatment with other anti-seizure drugs, PER was added in all cases (8, 16 and 12 mg) and cessation of SE was observed within the next 4-8 hours. All the cases involved a stroke-like lesion present on brain MRI.

In our patients, PER was an effective option in SE associated with MELAS syndrome.

1. Introduction

Epilepsy is commonly described in mitochondrial diseases. The types of epilepsy reported in both adults and children include myoclonic seizures, focal to bilateral tonic–clonic seizures, epilepsia partialis continua, and generalized epilepsy syndromes [1–3]. The prevalence of status epilepticus (SE) in these patients is unknown and it is reported less often than other types of seizures, although it may go unrecognized.

Within the spectrum of mitochondrial diseases, MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) is among those most commonly associated with SE. It was reported in 7.9% of cases in one series, and always in the context of a stroke-like episode [4].

Most SE episodes in mitochondrial diseases are refractory to treatment [2], and status persists despite administration of anti-seizure drugs (ASDs). In this scenario, the efficacy of GABA-ergic drugs is markedly reduced [5] and glutamate can play a major role in SE persistence by promoting perpetuation of the epileptic activity through AMPA receptors.

Perampanel (PER) is a selective, noncompetitive AMPA receptor antagonist that has emerged as a promising option for SE because of its particular pharmacodynamics. Knowledge on its use for managing SE is increasing [6] and a recent review of all published SE cases treated with PER has described highly variable efficacy. The review included 10 articles with 69 SE episodes [6], in which none of the causes was mitochondrial diseases. Here, we describe the first series of cases in which patients with mitochondrial disorders experienced SE and received PER treatment.

2. Case studies

2.1. Case 1

A 37-year-old man was admitted to our hospital for repetitive focal seizures with an occipital semiology. His history included genetically-confirmed MELAS syndrome (mtDNA m.3243A>G) with epilepsy, treated with lamotrigine (LTG). The electroencephalography (EEG) performed in the emergency department included lateralized periodic discharges with superimposed fast activity and rhythmic activity (LPDs + FR); and according to the ILAE classification [7], he was considered to have a non-convulsive SE (NCSE) without prominent motor symptoms (i.e., without coma, focal, and without impaired consciousness).

The patient was started on levetiracetam (LEV) and lacosamide (LCM) with no clinical or EEG improvement. L-Arginine, coenzyme Q10, and weight-adjusted methylprednisolone were then given successively in the first 24 h. As SE persisted, PER was added directly at 8 mg, without therapy escalation as has been done in other reports [6]. Six hours later, the patient had improved clinically, and an EEG monitoring

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showed resolution of the SE episode (Fig. 1). Shortly after cessation of SE, the patient underwent magnetic resonance imaging (MRI), showing a hyperintense area in the right occipital lobe consistent with metabolic infarction (Fig. 1). Hospitalization lasted 11 days with no need for intensive care unit (ICU) admission (Table 1), and recovery was favorable.

2.2. Case 2

A 19-year-old male who had epilepsy and known MELAS since childhood, (genetically confirmed: mtDNA m.3243A>G), was admitted to the emergency room for headache, photopsia, and loss of vision in the left visual hemifield. He was receiving LTG and clobazam to treat the epilepsy. The EEG showed an evolving ictal pattern in the right occipital region progressing in amplitude, morphology, and degree of sharpness, with sequential spread. This pattern was consistent with NCSE similar to the first patient. L-Arginine, coenzyme Q10, and weight-adjusted methylprednisolone were started. Clonazepam (CLZ) and LEV were the first drugs administered, followed by LCM. As there was no improvement, PER was administered at a dose of 16 mg without escalation. At 8 h following the start of PER, the EEG showed resolution of SE. MRI depicted a hyperintense area in the right occipital lobe consistent with a metabolic infarction. The duration of hospital stay was 60 days. This lengthy stay was not related to SE, but instead, to systemic problems associated with his underlying illness. ICU was not needed, and he was discharged with moderate disability (Table 1).

2.3. Case 3

A 39-year-old man was admitted for continuous visual symptoms in right hemifield. His history included a stroke-like lesion one year before causing a symptomatic epilepsy; he was diagnosed as MELAS during follow-up and he was being treated with LEV. Emergent EEG findings indicated non-convulsive SE with visual symptoms (occipital origin) and its features included LPDs + FR, similar to the findings in Case 1. L-Arginine and coenzyme Q10 were also started at admission. LCM was added to LEV with no clinical or EEG improvement. After confirming the lack of response, oral PER 12 mg was directly added to the treatment. SE resolved in the following 4 h, was verified with EEG, and no more clinical seizures were reported by the patient. A new lesion found on MRI was consistent with a stroke-like lesion associated with MELAS. The hospital stay lasted 6 days and recovery was excellent.

3. Discussion

We present a favorable experience with PER in the treatment of three cases of SE in patients with mitochondrial disorders. Information on patients with refractory SE treated with PER is increasing, but still limited, and there are no published data on its use in mitochondrial disorders. To our knowledge, these are the first cases of SE due to stroke-like lesions in MELAS treated with PER.

SE occurring in patients with mitochondrial disorders is usually resistant to anti-seizure drug treatment. In stroke-like lesions, clinical symptoms and EEG usually shows involvement of posterior brain regions, and the prognosis may be poor, with liver dysfunction and death [8]. Treatment of SE in mitochondrial disease has not been definitively validated [8], and there may be a limit to the therapy options, as many anti-seizure drugs used in SE pose a risk for MELAS syndrome and therefore, should be avoided or carefully monitored [9]. Examples of potentially risky anti-seizure drugs are benzodiazepines, phenobarbital, propofol, and valproate, which can lead to worsening of seizures and even multi-system damage.

Furthermore, recommendations are not straightforward for treating NCSE without impaired consciousness. In adults with NCSE independent of MELAS, after failure of a benzodiazepine (first-line therapy), an ASD is recommended as second-line therapy, and further non-anesthetic ASDs such as levetiracetam, phenobarbital, or valproic acid is recommended instead of intravenous anesthetics [10]. Therefore, this treatment uncertainty plus restrictions for the use of certain ASDs in MELAS may considerably reduce the available therapeutic strategies.

In our three patients, SE was confirmed by EEG, and SE cessation was established by clinical and EEG resolution of the previously documented ictal activity. A combination of several ASDs was used to treat refractory SE; hence, it may be difficult to establish a relationship between PER monotherapy and success in terminating the episode. However in our report, PER was the last drug introduced or increased in the 24 h prior to SE cessation, with no changes in concomitant medication; and this method is considered as the most appropriate measure for the evaluation of efficacy of an AED in the treatment of SE [11].

PER was well tolerated, with no adverse events recorded. Furthermore, oral administration enabled conservative management of SE associated with a stroke-like episode. Another point to consider is that it may be difficult to determine whether the improvement was related to other aspects of the treatment (e.g., L-Arginine or Q10 coenzyme administration), nonetheless, this concomitant treatment had been started before the ASDs, and there had been no response.

We cannot draw firm conclusions based on only three cases. It could be argued that the response may have been due to spontaneous resolution of a stroke-like episode or delayed effects of the previously administered anti-seizure medication. However, after use of 2 or 3 ASDs in refractory NCSE, the next step would be to consider use of anesthetics and intubation, and these cases show that PER could be an option to avoid the use of drugs already restricted in this group of patients. Another reason to use PER is that SE was refractory and long-lasting in all cases, and it is known that as epileptiform activity persists, SE becomes more resistant to GABAergic drugs, which could make drugs targeting AMPA receptors more appropriate. Of note, PER use was only directed to treat SE and was not used to treat the stroke-like episodes.

4. Conclusion

Management of patients with MELAS syndrome is difficult and there is no standardized treatment for the management of focal SE. Once stroke-like episodes begin, the clinical status of the patient may rapidly decline and multiorgan dysfunction can occur; hence, the importance of treating the epilepsy. The findings in our cases indicate that PER may be an effective option in SE associated with MELAS syndrome. Formal clinical trials in patients with various genetic causes of mitochondrial epilepsy would be the ideal method to ascertain the true efficacy of PER in these patients.

Conflict of interest

Dr. Santamarina reports grants and personal fees from UCB Pharma, personal fees from Esai, personal fees from Esteve, grants and personal fees from Bial, outside the submitted work; Dr. Abraira reports personal fees from UCB Pharma, outside the submitted work; Dr. Toledo reports grants and personal fees from UCB Pharma, personal fees from Esai, personal fees from Esteve, grants and personal fees from Bial, outside the submitted work; Dr. Salas-Puig reports grants and personal fees from UCB Pharma, personal fees from Esai, personal fees from Esteve, grants and personal fees from Bial, personal fees from Sanofi, outside the submitted work; Dr. Alpuente, Dr. Maisterra, Dr. Sueiras and Dr. Guzman have nothing to disclose.

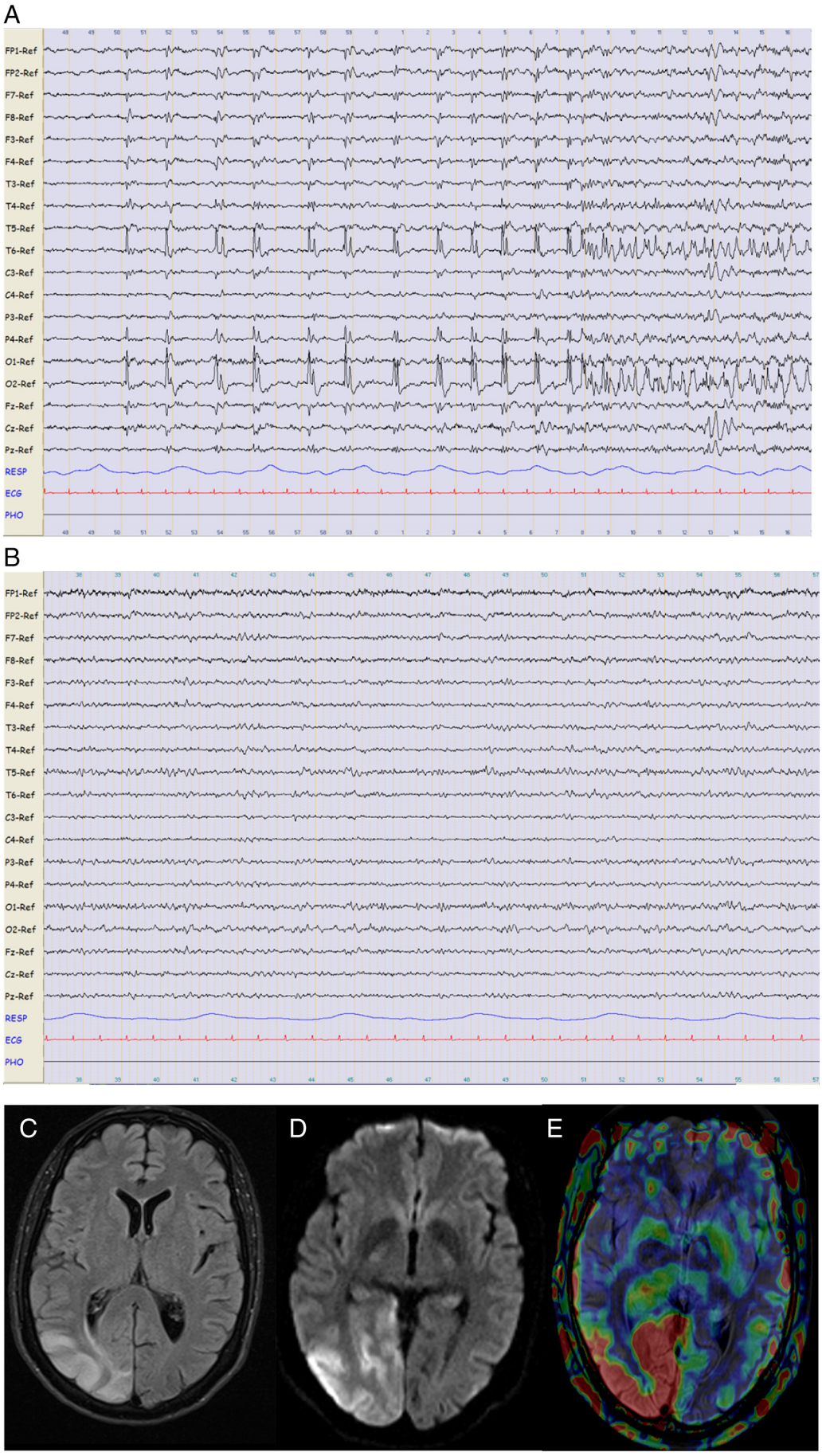
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Table 1
Patients' clinical data.

	Patient 1	Patient 2	Patient 3
Age, years	37	19	39
Preexisting epilepsy	Yes	Yes	Yes
Etiology	Stroke-like episode	Stroke-like episode	Stroke-like episode
SE type	NCSE without coma, focal	NCSE without coma, focal	NCSE without coma, focal
EEG pattern	LPD + F + R	Evolving, electrographic seizures	Evolving, electrographic seizures
STESS score	1	0	0
EMSE score	81	68	74
Initial dose PER, mg	8	16	12
Maximum dose PER, mg	8	16	12
GOSE scale	Good recovery (7)	Moderate disability (5)	Good recovery (7)
ICU stay	No	No	No
Hospital stay, days	11	60	6
Drugs used	LEV, LCM, PER	CLZ, LEV, LCM, PER	LEV, LCM, PER

Abbreviations. NCSE, non-convulsive status epilepticus; LPD, lateralized periodic discharges; +F+R, superimposed fast and rhythmic activity; AEDs, antiepileptic drugs; LEV, levetiracetam; LCM, lacosamide; PER, perampanel; CLZ: clonazepam; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology-based Mortality Score in Status Epilepticus; GOSE, Glasgow Outcome Scale-Extended; ICU: Intensive Care Unit.

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Ethical statement

Informed consent was obtained from subjects for publication. The privacy rights of all subjects have carefully been observed.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Fig. 1. Case 1. Initial EEG (a) and EEG 6 h after PER (b). Referential (common average) montage (sensitivity: 10 μV/mm; 0.5–70 Hz; 20-s epoch length). (a) Initial EEG shows SE with periodic discharges and superimposed fast and/or rhythmic activity (LPDs, LPDs + F, LPD + R, LPDs + FR). (b) EEG after initiation of PER shows absence of epileptiform discharges and background improvement with an asymmetric alpha activity. Axial FLAIR (C), DWI (D) and arterial spin labeling perfusion (E) MR images. The lesions in the right occipital lobe are seen as a hyperintense area on FLAIR and DWI. Hyperperfusion is showed in peripheral areas. These findings correspond to the stroke-like episode. Distribution of the stroke-like lesions is incongruent with a defined vascular territory and hyperperfusion is seen in the affected brain regions in patients with MELAS. LPD, lateralized periodic discharges; R= superimposed rhythmic activity; F= superimposed fast activity; FR= superimposed fast and rhythmic activity; FLAIR, T2-weighted fluid-attenuated inversion recovery; DWI, diffusion weighted imaging; MR, magnetic resonance.