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LETTER TO THE EDITOR

Eslicarbazepine acetate as therapy in hemifacial spasm☆

Acetato de eslicarbazepina como terapia en el espasmo hemifacial

Dear Editor:

Hemifacial spasm is characterised by chronic, involuntary, paroxysmal contractions of one side of the face. The disorder develops gradually, beginning with the orbicularis oculi muscle and progressively involving muscles of the lower half of the face. Although diagnosis is mainly clinical, we should rule out presence of vascular malformations or tumours at the emergence of the facial nerve (CN VII) from the brainstem using brain MRI and MRI angiography.[1] Most cases of hemifacial spasm correspond to primary forms. Compression of the facial nerve root by the anterior inferior cerebellar artery[1,2] is the most frequent cause, although other causes have also been described, including compression by veins,[3] other anatomical variants,[4] and brainstem lesions or arteriovenous malformations. Two different theories have been proposed to explain this phenomenon. The peripheral theory proposes that chronic irritation of the facial nerve nucleus or proximal nerve segment causes axon demyelination, resulting in ephaptic transmission of impulses and excessive firing of the facial nerve. The central theory, in contrast, postulates that irritation of peripheral facial nerve fibres induces excessive afferent (antidromic) activity, causing a functional reorganisation of synapses within the facial nucleus that results in abnormal firing of the nucleus.[1]

Chemodenervation with botulinum toxin is the treatment of choice due to its efficacy and safety profile, although it must be administered periodically and may cause adverse reactions. Botulinum toxin type A (BTA) acts at the neuromuscular junction, inhibiting the release of acetylcholine mediated by calcium channels through its interaction with SNAP25, a protein involved in vesicle fusion and acetylcholine release. This leads to local chemical denervation, causing transient, reversible muscle paralysis. The only definitive treatment, recommended in severe or refractory cases, is microvascular decompression. Oral medication is usually indicated in mild cases, patients unwilling to undergo BTA injection, and patients ineligible for surgery. Several trials have been conducted of anticholinergics, antipsychotics, and such antiepileptic drugs (AEDs) as carbamazepine (CBZ), gapabentin (GBP), and clonazepam, with inconsistent results.[1,5]

We describe the case of a 68-year-old woman with no relevant medical history who presented short-lived paroxysmal contractions of the left side of the face, involving the left orbicularis oculi, left levator anguli oris, and left mentalis muscles (Fig. 1; Appendix A, Supplementary data). Brain MRI and MRI angiography ruled out secondary causes (Fig. 2). We indicated monotherapy with eslicarbazepine acetate (ESL) dosed at 800 mg once daily; after achieving a clinical response, the dose was increased to 1200 mg, which achieved complete symptom resolution with excellent tolerance.

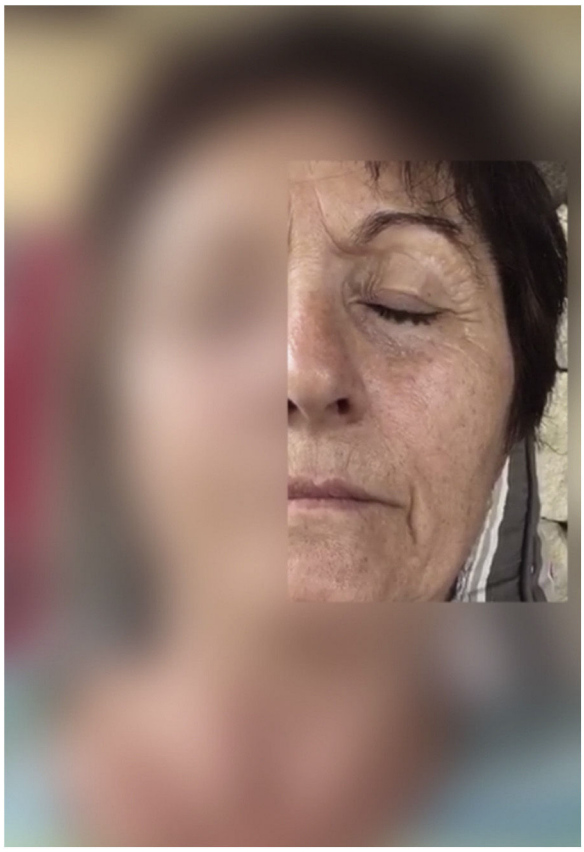

Figure 1 Symptoms of our patient: left hemifacial spasm, with elevation of the left eyebrow and mild twitching of the orbicularis oculi, levator anguli oris, and mentalis muscles, resulting in mild facial asymmetry.

This is the first reported case of hemifacial spasm responding to ESL. The literature includes reports of patients with paroxysmal kinesigenic dyskinesia,[6—9] chorea,[10] or hemifacial spasm secondary to mucopolysaccharidosis type II successfully treated with CBZ.[11] ESL has successfully been used for the treatment of vestibular paroxysmia following failure of GBP.[12] ESL is a third-generation AED approved in 2009 by the European Medicines Agency and in 2013 by the United States Food and Drug Administration, and has been available on the Spanish market since February 2011.[13] It is currently indicated as monotherapy for focal-onset seizures with or without secondary generalisation in adults with epilepsy, or as adjuvant therapy.[13,14]

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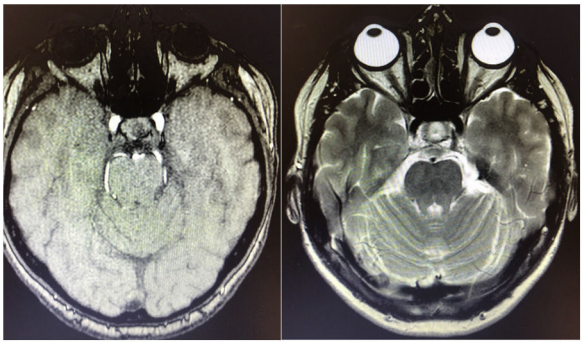

Figure 2 Brain MRI (axial plane). T1-weighted contrast-enhanced (left) and T2-weighted sequences (right) at the level of the pons, revealing no arteriovenous malformations or other structural lesions at the cerebellopontine angle.

ESL, CBZ, and oxcarbazepine (OXC) all belong to the dibenzazepine family. Interestingly, ESL selectively interacts with the inactive state of voltage-dependent sodium channels through slow inactivation (unlike CBZ and OXC) and inhibits hCaV3.2 inward currents with greater affinity than CBZ. Although these drugs are not indicated for the treatment of neuropathic pain, headache, or neuralgia, they are frequently used off-label in clinical practice. Several studies have reported favourable results in the treatment of trigeminal neuralgia, postherpetic neuralgia, and other cranial neuralgias with ESL,[13] with response rates of 88.9% for trigeminal neuralgia. Trigeminal neuralgia is characterised by demyelination of A-δ fibres; it has been hypothesised that paroxysmal attacks result from ectopic afterdischarges in damaged axons, triggered and amplified by ephaptic conduction and cross-excitation transmitted by afferent A-β fibres after trivial sensory stimuli. ESL suppresses ectopic discharges from hyperexcitable fibres by inhibiting voltage-dependent sodium channels in the slow inactivation phase. This theory may be extrapolated to hemifacial spasm, whose pathophysiological mechanism is similar to that of trigeminal neuralgia.[15] Pending further research, we believe that ESL may be an effective alternative in the treatment of hemifacial spasm.

Ethics approval

This study complies with the ethical principles of the Declaration of Helsinki. It did not require participation of the patient or performance of any invasive tests or techniques. No activity outside normal clinical practice was performed. The patient gave informed consent to use of her likeness and clinical data for research and training purposes.

Funding

None.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.nrl.2021.05.004.

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Hypercholesterolaemia treatment in a patient with family hypercholesterolaemia and myopathy due to carnitine palmitoyltransferase II deficiency with PCSK9 inhibitors☆

Tratamiento de la hipercolesterolemia en un paciente con hipercolesterolemia familiar y una miopatía por déficit de carnitina palmitoiltransferasa II con inhibidores de PCSK9

Dear Editor:

Carnitine palmitoyltransferase (CPT) deficiency is the most frequent metabolic myopathy.[1] This condition follows an autosomal recessive inheritance pattern, and presents with 2 phenotypes: the childhood-onset form (type I, hepatic CPT1 deficiency), and the adult-onset form (type II, muscle CPT2 deficiency). CPT2 deficiency typically presents between the 2nd and 3rd decades of life and is characterised by myalgia, cramps, weakness, and myoglobinuria with onset after a clear trigger event.[1,2]

These patients may present episodes of rhabdomyolysis triggered by prolonged exercise, infections, fasting, or the use of statins, among other factors.[1] Therefore, we should be very cautious when using statins to treat concomitant dyslipidaemia. A new family of drugs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, decreases blood low-density lipoprotein cholesterol (LDL-C) levels without the muscle toxicity of statins; therefore, they may be used in this type of patients.

The 2 currently marketed drugs (alirocumab [Praluent®] and evolocumab [Repatha®]) are 100% human monoclonal antibodies that selectively bind to PCSK9 and largely inhibit the degradation of LDL-C receptors; thus, by increasing the number of receptors, they reduce the level of LDL-C in the blood.[3] In Spain, the healthcare system only finances these drugs for the following indications: *1)* patients with established cardiovascular disease and LDL-C > 100 mg/dL despite maximally tolerated statin therapy or with contraindications for statin treatment; or *2)* patients with heterozygous familial hypercholesterolaemia (HFH) and LDL-C levels > 100 mg/dL despite maximally tolerated statin therapy or with contraindications for statin treatment.[4] We present the case of a patient with myopathic CPT2 deficiency and HFH that shows the relevance of the new PCSK9 inhibitors in the treatment of patients with muscle disorders contraindicating statin treatment. Our patient was 56-year-old woman with HFH who was referred to our clinic for assessment and treatment of dyslipidaemia. She had recently been diagnosed with CPT deficiency. She reported episodes of myalgia and weakness after effort since a young age. Furthermore, the patient had presented several episodes of rhabdomyolysis requiring hospital admission; the last was associated with the use of simvastatin, with creatine phosphokinase levels of 8262 U/L. The physical examination and blood analysis yielded normal results. An electroneurography/electromyography study and muscle biopsy revealed no pathological findings. A genetic study showed CPT2 deficiency (with a pathogenic mutation and a mutation of uncertain significance: c.338C>T, p.Ser113Leu and c.1892G>A, p.Arg631His). The lipid profile revealed cholesterol levels of 298 mg/dL; HDL-cholesterol: 59 mg/dL; LDL-C: 206 mg/dL; triglyceride level: 167 mg/dL. Considering the risk of rhabdomyolysis due to the use of statins, we started treatment with a PCSK9 inhibitor: 75 mg alirocumab, administered subcutaneously every 15 days. The patient presented a cutaneous adverse drug reaction to alirocumab, and we switched treatment to 40 mg evolocumab every 15 days. She is currently receiving the same treatment with good tolerance, with LDL-C levels below 100 mg/dL in the follow-up visits.

Statins are the cornerstone of pharmacological therapy for atherosclerotic cardiovascular disease. Although these drugs are safe, a considerable percentage of patients present muscular side effects, such as myalgia, cramps, weakness, and rhabdomyolysis.[3]

Although the incidence of rhabdomyolysis associated with statin treatment amounts to approximately 0.70 cases per 100 000 person-years, up to 29% of patients receiving statins present muscular symptoms.[5]

Furthermore, in patients with muscle disorders, statins may exacerbate symptoms or trigger previously silent conditions.

In fact, the incidence of underlying genetic muscle disorders in patients with rhabdomyolysis induced by statins may reach up to 25% of cases.[6]

One study including 135 patients with myopathies induced by lipid-lowering drugs and undergoing genetic studies revealed that 10% of patients presented mutations causing the most frequent metabolic myopathies (CPT2 deficiency, myophosphorylase deficiency [McArdle disease], and myoadenylate deaminase deficiency). Thus, the frequency of carriers of CPT2 deficiency and McArdle disease was 13 and 20 times higher, respectively, than in the general population.[7]

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