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M. Marín Gracia[a,b,*], Á.M. Gutiérrez Álvarez[c]

[a] *Sección de Neurología, Servicio de Medicina Interna, Hospital Santa Bárbara, Soria, Spain*
[b] *Instituto de Investigación Aragón, Zaragoza, Spain*
[c] *Servicio de Neurología, Complejo Hospitalario de Navarra, Pamplona, Spain*

* Corresponding author.
E-mail address: martamaringracia91@gmail.com
(M. Marín Gracia).

https://doi.org/10.1016/j.nrleng.2021.05.007
2173-5808/

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]

☆ Please cite this article as: Luque Linero P, Castilla-Guerra L, Rojas Marcos Rodriguez I, Rico Corral MA. Tratamiento de la hipercolesterolemia en un paciente con hipercolesterolemia familiar y una miopatía por déficit de carnitina palmitoiltransferasa II con inhibidores de PCSK9. Neurología. 2022;37:231—232.

Other genetic myopathies described in patients with statin intolerance include: glycogen storage disease type II (Pompe disease; acid maltase deficiency) and type IX (deficiency of glycogen phosphorylase kinase B), malignant hyperthermia (*RYR1*, *CACNA1S*), recurrent myoglobinuria (LPIN1 mutation), myotonic dystrophy type 1 (*DMPK*) and type 2 (*CNBP*), and MELAS syndrome.[8]

Furthermore, statins may adversely interact with such other neuromuscular disorders as myasthenia gravis, dermatomyositis/polymyositis, inclusion body myositis, and amyotrophic lateral sclerosis, among others.[7,8]

Therefore, while genetic myopathies are frequently underdiagnosed, they should be considered in patients presenting muscular symptoms associated with the use of statins, particularly when symptoms or elevated levels of muscle enzymes persist after statin withdrawal. In these cases, the use of PCSK9 inhibitors as an alternative to the traditional treatment enables proper control of LDL-C levels without the associated risk of myopathy.

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P. Luque Linero[a,*], L. Castilla-Guerra[a], I. Rojas Marcos Rodriguez[b], M.A. Rico Corral[a]

[a] *Unidad de Riesgo Cardiovascular, Servicio de Medicina Interna, Hospital Virgen Macarena, Sevilla, Spain*
[b] *Servicio de Neurología, Hospital Virgen del Rocío, Sevilla, Spain*

* Corresponding author.
E-mail address: Paula3.pl@gmail.com (P. Luque Linero).

https://doi.org/10.1016/j.nrleng.2021.05.006
2173-5808/

X-linked hereditary periventricular nodular heterotopia☆

Heterotopia nodular periventricular bilateral hereditaria ligada al cromosoma X

Dear Editor:

Periventricular nodular heterotopia (PNH) is a malformation of cortical development caused by impaired neuronal migration that prevents certain bundles of neurons from travelling from the marginal periventricular area to their final location in the cortex.[1] This creates nodules of ectopic grey matter that lead to erroneous connections, focal deficits, and frequently refractory epilepsy.[2]

PNH typically manifests in adolescence and may be associated with a wide range of symptoms; approximately 90% of patients will present epilepsy and cognitive delay. Depending on the mutation, PNH may also cause malformations in other systems, especially the cardiovascular system.[3]

Its worldwide prevalence is unknown due to the rareness of the condition. The available data were obtained from case series, with one providing data on adult patients with epilepsy[4]; approximately 2% of these patients have PNH, which accounts for 20% of cases of malformations of cortical development.

Regarding the aetiology of the condition, studies have identified mutations in specific genes that are responsible for neuronal migration to the cortex.[5] In particular, mutation of the *FLNA* gene, involved in the regulation of cell stability and motility through several biological systems, and which follows an X-linked dominant inheritance pattern,[6] is associated with higher fetal and perinatal mortality in males, with better outcomes in female patients. We should mention that the reported cases are frequently sporadic.[7,8]

Diagnosis is established by brain MRI, which typically reveals confluent masses of ectopic grey matter that are usually bilateral, isointense, and distributed throughout the area surrounding the lateral ventricles.[9] Furthermore, studies have also identified abnormalities in the corpus callosum, including hypoplasia, dysgenesis, and agenesis.[10] Electroencephalography studies reveal epileptogenic discharges at the level of the periventricular nodules or in the underlying cortex, or both simultaneously.[11]

Regarding treatment, surgical resection may be recommended in patients presenting seizures with specific, localised focal onset or displaying resistance to pharmacological treatment, after exhaustive evaluation.[12]

We describe the case of a 22-year-old woman with history of epilepsy of unknown aetiology since the age of 15. She was receiving treatment with phenobarbital and carbamazepine at optimal doses, without achieving adequate seizure control. At the time of assessment, she was 11.2 weeks pregnant with a single fetus. Her family history included seizures (her mother) during adolescence, which resolved after her first pregnancy.

Our patient was taken to the emergency department due to exacerbation of seizures; electroencephalography and metabolic, toxicity, and microbiology studies yielded normal results. Furthermore, a brain MRI scan revealed an irregularity in the contour of

☆ Please cite this article as: Angulo-Maldonado M, Lara-Sarabia O, Cadena-Bonfanti A, Ulloa-Piza A. Heterotopia nodular periventricular bilateral hereditaria ligada al cromosoma X. Neurología. 2022;37:232—234.