

depending on the existing enzyme level.<sup>5,6</sup> More recently, after analysing 27 genetic variations in the dihydrofolate reductase (DHFR), thymidylate synthase (TYMS), methylenetetrahydrofolate reductase (MTHFR), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC) and cyclin D1 (CCND1) genes, we reached the conclusion that variants in the MTHFR and DHFR genes might be considered as pharmacogenetic markers of response in patients with RA, and ATIC gene variants might be considered as toxicity markers.<sup>7</sup>

Nevertheless, we cannot fail to mention that pharmacogenetics has addressed the search for MTX toxicity and response predictors to MTX in a dissimilar manner. The different studies that have been published do not show coherent results, either due to the clinical heterogeneity of the sample, due to the differences in the way they define efficiency and toxicity, or due to the small size of the sample.<sup>8</sup>

Thus, we considered that, once the most frequent variables allowing us to predict beforehand favourable drug response or possible drug toxicity have been confirmed, the pharmacogenetic study should be routine to optimise the most efficient route of administration and dose. This consideration opens the door, in a not too distant future, to a personalised medicine for each patient that could be extended with the study of different therapeutic targets.<sup>9</sup>

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## Rhabdomyolysis Secondary to Physical Activity and Simultaneous Electrostimulation. A Case Report<sup>☆</sup>



### Rabdomiólisis secundaria a la realización de actividad física y electroestimulación simultánea: reporte de un caso

Mr. Editor:

We have recently assessed a 33-year-old female patient, an aerobic athlete who practises 180 min of swimming and 30 km (18.6 miles) of trotting per week, and who complained about proximal weakness and pain in lower limbs associated with noticeable volume increase in both thighs, of one day of evolution. Patient did not have any medical history of interest and was not taking any medication. The day before, she had used, for the first time, an electrostimulation device on the painful area while performing her regular exercises, which involved running on a treadmill for 30 min. The device consisted of short pants with electrodes for muscle stimulation of both glutei. The program used by the patient had a frequency of 50 Hz in accordance with the manufacturer's data sheet. The patient presented pain on palpation in quadriceps and lateral heads of triceps brachii and she showed proximal weakness that conditioned her pace. From the analytical point of view, she showed normal renal function, creatine phosphokinase (CPK) of 64,150 U/l, lactate dehydrogenase (LDH) 616 mg/dl, glutamate pyruvate transaminase (GPT) 640 U/l, glutamate-oxalacetate transaminase (GOT) 1050 U/l and myoglobinuria ++/+++. She was

treated with overhydration and bed rest for 3 days, after which the pain ceased significantly; the thighs volume was reduced, the myoglobinuria disappeared and the CPK descended to 1222 U/l. Two months later, all analytes were normalised and the patient went back to her regular sport activity without presenting new symptoms until after 6 months from the episode. Approximately 3 months after the episode, she had an electromyography done which did not identify a pattern compatible with neuropathy or myopathy. A lactate test was performed with normal results.

Post-exercise rhabdomyolysis is a process that can present itself in healthy subjects or in patients with metabolic muscular diseases. It is characterised by a lysis of the musculoskeletal striated fibre after physical exertion that manifests itself clinically as the triad of myalgia, weakness and choloria.<sup>1–3</sup> Its management is mainly support-oriented, and it consists of athletic rest and overhydrating to prevent renal failure secondary to myoglobinemia.<sup>4,5</sup> In scientific literature, there is only one case of rhabdomyolysis associated with the use of an electrostimulation device in a young male patient who was exposed to such device for several weeks.<sup>6</sup> Electrostimulation devices allow the performance of passive physical exercise through electrodes that generate isometric contractions in specific muscle areas.<sup>7</sup> These devices are available for domestic use and at gymnasiums since their popularity lies on the promise of physical conditioning without the need of performing voluntary physical exertion. Our patient was exposed to electrostimulation once, which is a fact that stands out when comparing her case with the one described in 2004 by Guarascio et al.<sup>6</sup> However, our patient performed her regular aerobic routine while carrying the electrostimulation device in both thighs. The complete analytical normalisation, the electromyographic study, the normality in the lactate test and the reincorporation to regular physical activity reasonably rule out that the patient suffers from any

<sup>☆</sup> Please cite this article as: Guillén Astete CA, Zegarra Mondragón S, Medina Quiñones C. Rabdomiólisis secundaria a la realización de actividad física y electroestimulación simultánea: reporte de un caso. *Reumatol Clin.* 2015;11:262–263.

muscular metabolic disease. The main risk factors associated with the development of rhabdomyolysis are lack of physical conditioning and the performance of extreme muscular exertion.<sup>8</sup> Our patient was a young woman who was used to physical activity. However, in our opinion, the use of a muscle electrostimulator while performing physical activity may generate tensile strengths capable of provoking the disruption of the muscle fibre's integrity with the well-known consequences. Due to lack of more cases, we cannot establish a universal recommendation advising against the use of electrostimulators. Nevertheless, common sense suggests that their use should not be made while performing active exercises.

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## “Benign Hypermobility”-Hyperlax Ehlers–Danlos Syndrome. Other Comorbidities<sup>☆</sup>



### «Hipermovilidad benigna»-síndrome de Ehlers-Danlos hiperlaxo. Otras comorbilidades asociadas

Dear Editor,

Nowadays, there are 11 different types of Ehlers–Danlos syndrome described. Types I and II (classic Ehlers–Danlos) and mainly type III are classified as benign hypermobility.

When studying this syndrome, we noticed that the word “hiperlaxitud” (hypermobility) does not exist in the dictionary of the Real Academia de la Lengua (Royal Spanish Academy). The concept of “hypermobility” refers to the articular hypermobility observed in these patients, causing painful symptomatology. As shown in the recent article of Pantoja et al.,<sup>1</sup> a score higher than 4 in Beighton's test<sup>2</sup> is the essential criterion for the diagnosis of this pathology, along with the presence of pain.

In the first International Symposium on Ehlers–Danlos syndrome, which took place in Ghent in September, 2012, an attempt was made to establish new diagnostic criteria that would offer higher specificity than the old criteria of Brighton and Villefranche.<sup>3</sup> These new criteria must allow for the inclusion of truly hiperlax forms and the obtainment of universally accepted instruments for the measurement of laxity, not only articular but also from other tissues, avoiding professional subjectivity in the assessment of mainly cutaneous involvement<sup>4</sup> (more or less flexible, silky, etc.).

The first inclusion criterion to be able to diagnose a patient of this pathology is that the patient is over 16, because, physiologically, tissue laxity is greater during childhood. Furthermore, it is important to point out that, physiologically, tissue laxity is higher in women than in men. This pathology usually affects women, as occurs among main connective tissue diseases.

The most interesting data we have gathered in our hypermobility/Ehlers–Danlos syndrome unit during the last 3 years is the following:

- Out of 23 patients diagnosed with articular laxity, 3 of them were men and 20 were women. The average age of our patients was 33 years. Out of the 23 patients, 18 (78%) were subjected to at least one musculoskeletal surgical intervention or due to peripheral nerve entrapment. Of those 18 patients, 11 needed reintervention of the same pathological process. The surgical interventions average was 3 per patient, and there was one specific case of a patient who was subjected to 13.
- Affectionate-emotional disorder was observed in 14 patients (60%). Of those, 3 had attempted suicide.
- In 5 patients (22%), low tension figures were observed and/or there were episodes of vasovagal syncope, in relation to the dysautonomia. In 6 patients (26%) a clear Raynaud's phenomenon with its 3 phases was observed. Autoimmune diseases were discarded for all of them. We observed livedo reticularis in 2 patients. Vitamin D3 deficit was identified in 17 patients (74%). We have not performed densitometric studies on our patients; therefore, we cannot provide data about the potential greater incidence of osteoporosis in subjects with this pathology, as pointed out in studies.<sup>5,6</sup> We have not studied how many patients presented fibromyalgia or chronic fatigue syndrome criteria<sup>7</sup> either.

As well-indicated in the section “Clinical Rheumatology in Images”, it is of interest to rheumatologists and other experts who assess musculoskeletal pathology to know the necessary information in order to diagnose “benign hypermobility” syndrome<sup>8</sup> and rule out the possible presence of a vascular form or type IV, which is associated to visceral aneurysmal malformations.<sup>4,9</sup> This vascular type is rare and difficult to diagnose and requires confirmation through genetic tests. Likewise, it is important to know the presence of comorbidities and the high rate of failed surgical interventions that are observed in patients with benign hypermobility, aspects to be taken into account in case of requiring management in surgical units.

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<sup>☆</sup> Please cite this article as: Turrión Nieves AI, Moruno Cruz H, Martín Holguera R, Sánchez-Atrio AI. «Hipermovilidad benigna»-síndrome de Ehlers Danlos hiperlaxo. Otras comorbilidades asociadas. *Reumatol Clin.* 2015;11:263–264.