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Muscle imaging in muscle dystrophies produced by mutations in the *EMD* and *LMNA* genes

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Abstract

Identifying the mutated gene that produces a particular muscle dystrophy is difficult because different genotypes may share a phenotype and vice versa. Muscle MRI is a useful tool to recognize patterns of muscle involvement in patients with muscle dystrophies and to guide the diagnosis process. The radiologic pattern of muscle involvement in patients with mutations in the *EMD* and *LMNA* genes has not been completely established. Our objective is to describe the pattern of muscle fatty infiltration in patients with mutations in the *EMD* and in the *LMNA* genes and to search for differences between the two genotypes that could be helpful to guide the genetic tests. We conducted a national multicenter study in 42 patients, 10 with mutations in the *EMD* gene and 32 with mutations in the *LMNA* gene. MRI or CT was used to study the muscles from trunk to legs. Patients had a similar pattern of fatty infiltration regardless of whether they had the mutation in the *EMD* or *LMNA* gene. The main muscles involved were the paravertebral, *glutei*, *quadriceps*, *biceps*, *semitendinosus*, *semimembranosus*, *adductor major*, *soleus*, and *gastrocnemius*. Involvement of *peroneus* muscle, which was more frequently affected in patients with mutations in the *EMD* gene, was useful to differentiate between the two genotypes. Muscle MRI/CT identifies a similar pattern of muscle fatty infiltration in patients with mutations in the *EMD* or the *LMNA* genes. The involvement of *peroneus* muscles could be useful to conduct genetic analysis in patients with an EDMD phenotype.

Keywords: Emery–Dreifuss; *LMNA*; *EMD*; Muscle MRI; Muscle CT; Muscle dystrophy

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1. Introduction

Mutations in the *EMD* and *LMNA* genes cause different types of muscle disease. These two genes codify for three proteins – emerin, lamins A and C – located in the inner nuclear membrane. Mutations in the *EMD* gene have an X-linked recessive inheritance and are responsible for three disorders: Emery–Dreifuss Muscle Dystrophy (EDMD) type 1, isolated cardiomyopathy, and sinus node dysfunction [1]. Mutations in the *LMNA* gene can be inherited as a dominant or recessive trait and cause a wide spectrum of diseases involving skeletal muscle, heart, bone, peripheral nerves, or fat [2]. Muscle disorders caused by mutations in the *LMNA* gene can manifest as many phenotypes such as limb girdle muscle dystrophy 1B (LGMD-1B), quadriceps myopathy with dilated cardiomyopathy, congenital muscle dystrophy, autosomal dominant EDMD type 2, or autosomal recessive EDMD type 3 [3–5].

EDMD is characterized by muscle weakness involving humeral and peroneal muscles, prominent contractures of elbows, ankles and spine, and cardiac conduction defects and/or cardiomyopathy [1,6]. There are no major clinical differences in these patients regardless of whether the gene that causes the disease is the *EMD* or the *LMNA* [7]. However, it is not known if these patients have a different clinical progression or if they have differences in the muscle pattern involvement when studied with muscle MRI depending on which gene is mutated [5].

In the last years, several authors have used MRI or CT to determine the patterns of muscle fatty infiltration in muscle dystrophies [8–11]. Recognition of particular patterns of muscle involvement is helpful to conduct differential diagnosis of these diseases and may be also used to study the natural history of the diseases and even evaluate the results of potential therapeutic interventions. It has been previously described that the *vasti*, the posterior muscles of the thighs and the posterior muscles of the legs could be involved in patients with mutations in the *LMNA* and *EMD* genes [8,12]. However, the pattern of muscle fatty infiltration varies widely depending on the publication reviewed and it is unknown at present whether muscle MRI or CT scan could differentiate between EDMD caused by mutations in the *EMD* or in the *LMNA* gene [13–16].

Our objectives were to describe the clinical and radiological characteristics of a large cohort of patients with muscle disease produced by mutations in the *EMD* and *LMNA* genes and to search for differences between the two genotypes that could guide genetic analyses in patients with EDMD phenotype.

2. Material and methods

2.1. Patients

We conducted a national, multicenter descriptive study in five neuromuscular centers in Spain. All patients with mutations in the *EMD* or *LMNA* genes were considered for inclusion in the study. We also included five asymptomatic relatives of patients with mutations in the *LMNA* gene who had undergone genetic counseling. The Ethic Committee of Hospital de la Santa Creu i Sant Pau in Barcelona reviewed and approved the protocol. All participants signed an inform consent to take part in the study.

We recorded demographic data (age and gender) and clinical data (age at onset of symptoms, age at diagnosis, type of inheritance, presence of contractures, and muscle pain or muscle weakness involving axial, proximal and distal muscles of the limbs). We also analyzed heart rate disturbances, including the need for pacemaker implantation or cardioverter-defibrillators. Table S1 provides a summary of the patients included.

Patients with mutations in the *EMD* and *LMNA* genes were divided into 4 groups according to their clinical phenotype:

- Emery–Dreifuss (EDMD): patients with a phenotype characterized by humero-peroneal weakness and contractures.
- Limb girdle muscle weakness (LGMD): patients with girdle weakness at the onset of the disease, with or without prominent contractures.
- Isolated cardiomyopathy: patients with isolated cardiac dysfunction related to mutations in the *EMD* or *LMNA* gene, without evidence of muscle weakness or contractures at clinical examination.
- Asymptomatic carriers: patients without muscle weakness, joint contractures or heart disease studied for genetic counseling.

2.2. Muscle imaging

Muscle MRI was performed in 19 patients and CT scans were performed in 23 patients with contraindications for MRI. Muscle MRI was performed in a 1.5T Philips Intera or a 1.5T Philips Achieva XR depending on the centers. We obtained T1-weighted spin-echo axial images from the mid-dorsal segment to the feet. The parameters used for MRI were TR = 300 ms, TE = 10 ms, thickness = 10 mm. CT exams were performed with a 16-section equipment (Brilliance CT 16-Slice; Philips) in all the centers and included axial images and coronal reconstructions. The parameters used for CT were 140 kV and 120–350 mA. Section thickness was 1.25 mm, with a section interval of 0.6 mm. The axial images were 5 mm thick, with an increment of 5 mm in every slide.

Two independent observers, blind to clinical data, quantified fatty muscle infiltration in muscle MRI and CT using the modified version of the Mercuri score described by Dr. Fischer [17]. This score has been previously used to quantify muscle fatty infiltration in both muscle CT and muscle MRI:

- Normal muscle appearance: 0 points
- Mild infiltration: traces of increased signal intensity on the T1-weighted MR sequences: 1 point
- Moderate infiltration: increased T1-weighted signal intensity with beginning confluence in less than 50% of the muscle: 2 points
- Severe infiltration: increased T1-weighted signal intensity with beginning confluence in more than 50% of the muscle: 3 points
- End-stage appearance: entire muscle replaced by increased density of connective tissue and fat: 4 points