Utility of magnetic resonance imaging in the diagnosis of hereditary muscle diseases


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Abstract: Hereditary muscular diseases are rare disorders, due to a genetic defect that causes an alteration in the structure or function of the muscle fibers. They may present at any stage of life and their definitive diagnosis usually requires muscle biopsy. While the most frequent hereditary myopathies have a relatively characteristic clinical presentation, there is a substantial part thereof in which the symptoms are non-specific and the definitive diagnosis may take a long time. Magnetic Resonance Imaging (MRI) has earned a place in the diagnostic process of this last group of myopathies, confirming the presence of muscle involvement and raising diagnostic approaches based on its distribution, information that guides the immunohistochemical and/or genetic study necessary for the definitive diagnosis. In this article we review the basic study protocols with MRI of the myopathies and their interpretation, also showing some cases of these diseases.

Keywords: Hereditary, MRI, Myopathies.

Resumen: Las enfermedades musculares hereditarias son patologías raras, debidas a un defecto genético que causa una alteración en la estructura o funcionamiento de las fibras musculares. Pueden debutar en cualquier etapa de la vida y su diagnóstico definitivo suele requerir de biopsia muscular. Si bien las miopatías hereditarias más frecuentes tienen una presentación clínica relativamente característica, existe una parte importante de ellas en que los síntomas son poco específicos y su diagnóstico definitivo puede tomar largo tiempo. La resonancia magnética (RM) ha ganado un espacio en el proceso diagnóstico de este último grupo de miopatías, confirmando la presencia del compromiso muscular y planteando aproximaciones diagnósticas en base a su distribución, información que acota el estudio inmunohistoquímico y/o genético necesario para el diagnóstico definitivo. En el presente artículo revisaremos los protocolos de estudio básico con RM de las miopatías y su interpretación, mostrando también algunos casos de estas enfermedades.

Palabras clave: Hereditario, Miopatías, RM.


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Introduction

Striated muscle may be affected by pathologies of various origin. Most often an “acquired” condition occurs, among which we find trauma, infections, drug and autoimmune process affections(1).

However, there are also hereditary muscle diseases, which are primary diseases of the muscle, due to a genetic defect that causes an alteration in the structure or function of the muscle fibres. They are complex diseases both in their identification and management, therefore it is essential to have a high degree of clinical suspicion to consider their diagnosis(2). Hereditary muscle diseases present involvement patterns of the muscles that can be very characteristic and assist in their identification (e.g. Facioscapulohumeral muscular dystrophy). These patterns of muscle involvement that can be clinically identified, are also susceptible to analysis by imaging tests.

Traditionally, the specific diagnosis for the type of hereditary muscle disease requires a muscle biopsy (including immunohistochemistry study) in
most cases, which allows the genetic study to be guided in search of the mutation. In recent decades, magnetic resonance imaging (MRI) has become a fundamentally important diagnostic tool in the diagnostic process of myopathies that have a not so typical clinical presentation, demonstrating the involvement of certain muscle groups that guide the biopsy and pose diagnostic approaches that verify the immunohistochemical and/or genetic study\textsuperscript{(2-4)}.

**Hereditary muscle diseases**

**Definition**

Hereditary muscle diseases are a large group of more than 300 rare genetic diseases that result from mutations that affect the structure and function of muscles, and of variable transmission (autosomal dominant, autosomal recessive, X-chromosome linked, etc.)

**Classification and physiopathology**

The various hereditary muscle diseases can be classified into 16 groups, that are related to the primary defect in the genome. Some of these groups are: muscular dystrophies, congenital myopathies, distal myopathy, myotonic syndromes, among others\textsuperscript{(5)}.

They could also be divided using broad characteristics, into congenital, metabolic and muscular dystrophies:

- Congenital myopathies are those in which a failure occurs in the development of the muscle, leading to a structural defect thereof. These are grouped according to the histopathological pattern predominant in the biopsy. Examples of diseases in this group are X-linked myotubular myopathy, centronuclear myopathies (AD or AR), nemaline myopathy, among others\textsuperscript{(6)}.

- In metabolic myopathies the defect is functional, product of an enzyme failure in the metabolism of carbohydrates, lipids or mitochondrial respiratory chain. Examples of this group are glycogenosis type II or Pompe disease, the primary carnitine muscular deficiency and progressive external ophthalmoplegia\textsuperscript{(6,7)}.

- Muscular dystrophies are slow or rapidly progressive diseases, characterized by a pattern of necrosis-regeneration of the muscle fibres in the biopsy. This process is secondary to the alterations which the pathogenic mutation generates in the quantity or quality of various muscle protein (dystrophin, Caveolina, dysferlin, Lamin, etc.). The most common among these diseases are Duchenne and Becker dystrophies caused by the complete or partial absence of dystrophin, being less common among the dystrophies a very heterogeneous group known as girdle muscular dystrophies (LGMD-limb girdle muscular dystrophy)\textsuperscript{(2)}.

**Clinical context**

Hereditary muscle diseases can manifest in different stages of life, from birth to adulthood:

- Congenital myopathies are usually present at birth or in the first year of life with hypotonia, muscle weakness and delayed motor development. However, in some cases the first symptoms and signs may only become evident in adulthood\textsuperscript{(6)}.

- Similarly, metabolic myopathies may present immediately after birth until adulthood, with varying degrees of involvement that goes from hypotonia at birth, with death in the first years of life, until a symptom of just an increase in the muscle creatine phosphokinase (CPK) or intolerance to exercise. Some of these forms may be associated with cardiac or liver involvement\textsuperscript{(6,7)}.

- Muscular dystrophies can be congenital (with severe hypotonia and weakness from birth), of early onset (within the first decade of life) or later (after the second decade of life and still even after fifty years). Most normally there are no abnormalities at birth and later muscle weakness of varying distribution develops according to which disease it is about\textsuperscript{(6)}.

**Diagnosis**

Classically the diagnosis of hereditary muscle diseases has been based on the clinical characteristics, laboratory parameters (increased CPK), muscle biopsy (including immunohistochemical, electron microscopy and molecular biology study) and genetic studies\textsuperscript{(4,8)}.

Imaging studies have gained increasing importance in the diagnostic algorithm of myopathies, especially in the last decade. While the muscles can be evaluated with ultrasound, CT and MRI, it is the latter technique that gives us more complete and objective information. Following we will discuss how MRI studies should be conducted, what is the useful information they provide and how it is a diagnostic aid for the clinicians who evaluate these patients\textsuperscript{(9)}.

**MRI evaluation**

MR evaluation of hereditary muscle diseases has been performed for around 20 years with simple protocols that have scarcely changed to the present day. The different myopathies tend to selectively affect certain muscle groups and respect others more or less consistently, giving characteristic involvement patterns. However, the complexity of interpretation lies in the large number of existing diseases (and thus the patterns of involvement),
which determines some overlap of these patterns, to which is added the continuous description and introduction of new diseases.

**Study protocols**

As noted above, the basic protocols for the diagnosis of myopathies by MR are simple and have undergone little change since they were implemented.

In 1998 Mercuri and colleagues initiated an evaluation program with MR of children with muscular dystrophy using T1, T2 and STIR weighted sequences in the axial and coronal planes in arms and legs. Over time it has been shown that the plane of greatest utility in the evaluation is the axial and the most useful sequence is the T1 weighted. This is because the axial plane allows a better topographic evaluation of the muscle involvement and the adipose replacement areas in the muscle are better demonstrated on T1. STIR generates complementary information showing the degree of edema and/or inflammatory changes in the muscles, which theoretically correspond to the earliest changes in these diseases. Finally, the body segments most studied are the buttocks region, thighs and legs, as the information obtained in these places is usually enough to give a diagnostic orientation.

The current consensus suggests performing T1-weighted images in the axial plane, adding the coronal plane if you have the option of whole-body MRI. These sequences allow evaluation of adipose tissue infiltration of the muscles, a finding that is the marker for progression of the neuromuscular diseases, as well as their distribution, which allows us to verify diagnostic possibilities. The presence of edema and inflammatory changes can be detected with T2 weighted, T2 fat-suppressed or STIR sequences, studying the same areas as the T1-weighted sequences. The technical details for the 1.5T axial studies are summarized in table I.

Moreover they are using measurements of T2 relaxation time as a more objective way to estimate muscle edema, which is a more sensitive, accurate and reproducible, particularly useful method for research. To monitor the progression of fatty infiltration, performing proton density sequences with fat-water separation has been proposed, which would be a quantitative method compared to the T1-weighted sequences.

The techniques of spectroscopy and perfusion using MRI have so far been poorly evaluated, still remaining in the experimental stages, therefore these should not be considered in the routine protocols.
Interpretation

The analysis of the T1-weighted images is fundamental, and as already mentioned, can confirm the presence or absence of fatty infiltration. In order to systematize the degree of involvement, multiple classification scales have been proposed, of which we show two examples that are presented in Tables II and III(11).

However, at the diagnosis stage of these diseases, analysis of the involvement distribution is much more important than its severity. It is finally this that allows the consideration of differential diagnosis that are helpful to guide the immunohistochemical and genetic studies of these patients. In this context let us remember that there are dozens of inherited myopathies, in many of which the clinical signs are unspecific and do not allow an accurate syndromic diagnosis, in addition the laboratory studies that certify their diagnoses are difficult to perform and interpret. That's why reducing the range of possible diagnoses to rule out, will help to reach a positive diagnosis more quickly(11,12).

For their part T2FS or STIR sequences have the value to show muscle edema, which is a change that precedes the eventual fatty degeneration. In addition, they are useful in controlling the activity of the disease, such as therapeutic monitoring and as guidance for biopsy(19). In the diagnostic phase their information is mainly considered complementary to that provided by the T1-weighted images.

On reviewing the literature published of the MRI findings in different hereditary myopathies we will find numerous studies and extensive information. Based on these it has been possible to learn what is the pattern of fat infiltration distribution that follows each disease, which in some cases may be similar among certain myopathies if the test is evaluated in general. That is why specific involvement details which allow the narrowing down of the differential diagnoses are also described, which can be the involvement or in regard to any particular muscle, as well as the morphology of fatty infiltration within the same muscle.

Finally, it is of high important to contact the clinician, as their information is essential to guide and support the diagnoses that may arise based on the images.

Clinical cases

Below we present examples of five cases of hereditary muscle disease where MRI has been of diagnostic utility.

1. Disferlinopathy (Figure 3a and 3b)

The mutation in the dysferlin gene generates a girdle dystrophy that may have a pattern of involvement in either predominantly proximal lower limbs (girdle dystrophy type 2B, LGMD2B) or distal (Miyoshi distal...
myopathy, MM) at the start of the disease. With the progression of the disease, both phenotypes often overlap. In the thighs an involvement that predominates in the adductors and hamstrings is observed, and in the legs there is a greater involvement of the gastrocnemius and soleus. Muscle involvement may develop asymmetrically\(^{11,13,15}\).

2. Sarcoglycanopathy (Figure 4a and 4b)

This also ranks among the girdle dystrophies, identifying at least four types (LGMD2C-2F). In the thighs there may be severe involvement in both the anterior and posterior compartments, predominantly the anterior compartment, however a characteristic feature is the scarce involvement of the leg muscles. Published scientific literature concerning MRI findings for this specific group of myopathies is still limited. The images shown correspond to a gamma-sarcoglycanopathy (LGMD2C)\(^{11,12,15}\).

3. Nemaline myopathy (Figure 5a and 5b)

This belongs to the group of congenital myopathies and owes its name to the fact that in the histological studies, structures called nemaline bodies are found. Congenital myopathies are clinically very similar with each other, however, differences in appearance have been described on MR. In this case we can see diffuse involvement of the thigh and leg muscles, with the presence of multiple foci of fatty infiltration, however, there is a greater involvement of the sartorius and the anterior compartment of the leg (arrows)\(^{12,14,16}\).

4. Desminopathy (Figure 6a and 6b)

This belongs to a group known as myofibrillar myopathies that are caused by mutations in different genes (desmin, myotilin, Filamin C, etc.) that are characterized ultrastructurally by myofibrillar degeneration. The desminopathy is caused by mutations in the desmin gene (DES) and can be classified as myofibrillar, distal myopathy or girdle dystrophy 1E according to their clinical presentation. In the thighs
of patients with desminopathy the semitendinosus muscle is the most involved, along with the sartorius and gracilis, and in the legs involvement tends to dominate at the level of the peroneus (arrows)\(^\text{11}\).

**Figure 6.** Desminopathy. Axial T1-weighted images at thigh level (a) and legs (b). It highlights the greater involvement of the semitendinosus, sartorius and gracilis in the thigh and peroneus in the legs (arrows).

**Figure 7.** Bethlem disease. Axial T1-weighted images at thigh level (a) and legs (b). This myopathy describes a ring of fatty infiltration in the periphery of the vastus muscles and a fatty infiltrated plane between the gastrocnemius and soleus (arrows).

5. **Bethlem Disease (7a and 7b)**

This is a myopathy caused by mutations in the collagen VI gene. In the thighs of these patients it is described that the vastus muscles have a ring of fatty infiltration in the periphery, a finding known as concentric atrophy and in the legs a plane of fatty infiltration was observed between the gastrocnemius and soleus (arrows)\(^\text{11,12,14,15}\).

**Conclusions**

Currently, MRI has earned a place in the diagnostic process and control of hereditary muscle diseases. These are rare diseases, whose diagnosis can be difficult even in the hands of experienced clinicians. In this context, MRI can provide information that goes beyond demonstrating the existence of muscles with signs of myopathy, but may suggest differential diagnoses that guide specific histopathology, molecular biology and finally genetic studies that certify a definitive diagnosis. Given the difficulties and the high cost that laboratory studies have in our midst, muscle MRI becomes a fundamental tool in the diagnostic algorithm of myopathies. MRI has the advantage of being a non-invasive and relatively lower cost method, which can be applied massively for research and diagnostic orientation of myopathies. Study protocols for diagnosis are simple to implement, although there also exists advanced techniques that allow quantification of involvement that are particularly useful in controlling the progression of the disease.

**Bibliography**


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