Muscle involvement in inherited neuromuscular disease - imaging protocol and findings

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Authors: M. Baptista¹, P. Alves²; ¹Beja/PT, ²Lisbon/PT
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Learning objectives

1. To discuss the imaging methods used to study muscle involvement in inherited neuromuscular disease

2. To discuss the MRI protocol used for muscle evaluation in inherited neuromuscular disease

3. To discuss the patterns in inherited neuromuscular disease

Background

The motor unit is composed by a motor neuron that innervates muscle fibres through the neuromuscular junction. The motor axon extends from the anterior horn of the spinal cord or the brain stem in a peripheral nerve to innervate a group of fibres.

Neuromuscular disorders are characterised according to the site of injury within that unit. Spinal muscular atrophies occur due to motor neuron lesions and peripheral neuropathies develop due to axon lesions. When the muscle itself is affected the disease is classified as a primary myopathy, the best known of which are the muscle dystrophies.

Genetic neuromuscular disease represent a serious problems, especially in the paediatric population, as these can be deadly and have no known treatment. Moreover, an excess of 100 genetically distinct neuromuscular disease have been described in the last decades. (1,2)

Imaging findings OR Procedure Details

1. Imaging in the study of neuromuscular disease

The patient evaluation in the context of neuromuscular disease starts with a clinical history, neurological exam, blood tests and electromyography. Imaging is relevant in assessing the muscle pattern of involvement, which helps support the clinical findings, limit the differential diagnosis and guide muscle biopsies. (1-3)
On imaging, the striated muscle appearance varies according to several factors. One of the most relevant is patient age. Before puberty muscle bulk increases rapidly and is unaffected by gender; after puberty the sexual hormones lead to bulkier muscles in males. The peak muscle mass is reached between the ages of 25-40 years, with subsequent decline. The influence of age varies according to muscle group. (3)

Thirty years ago, Heckmatt et al described the value of ultrasound (US) in identifying the affected muscles in neuromuscular disease. The changes described in primary myopathy include increased muscle echogenicity and increased ratio between the subcutaneous tissue and the muscle belly, which translates the degree of denervation atrophy.(2)

Nowadays US continues to be useful and is a validated method of muscle assessment with high temporal resolution. Even though this is an operator dependent technique with low intra and inter-observer agreement, it is relatively inexpensive, does not use ionizing radiation and allows muscle involvement mapping in infants and small children. However, if the most superficial muscles are severely affected the study of deeper muscle groups is made harder due to decreased visualization secondary to sound wave attenuation. (2,3) This technique also allows functional imaging, with assessment of movement and documentation of pathologic fasciculations. Rating scales to determine level of fatty muscle replacement as well as computer-assisted assessment of muscles on US have been described. (4) US is particularly useful in infants and young children that would require general anaesthesia to undergo MRI. The sensitivity varies according to the illness from 25% in non-dystrophic myopathies to 100% in dystrophic myopathies. (3)

In the past, computer tomography (CT) was used to assess muscle changes (1-3) however due to the inferior soft-tissue contrast and the use of ionizing radiation, this technique was replaced by magnetic resonance imaging (MRI). MRI allows earlier detection of fatty muscle infiltration and provides better anatomical detail. It also identifies muscles oedema, which is not visible on CT.

MRI enables a quantitative assessment of muscle involvement classified as hypertrophy / pseudo-hypertrophy versus atrophy with or without fat infiltration. Patterns of involvement and the type of involvement help to differentiate or decrease the number of differential diagnoses. MRI is nowadays the most widely used imaging method in neuromuscular disease.

2. Magnetic Resonance Imaging protocol & findings

The young age of the patients being diagnosed with these conditions demands the use of a MRI protocol that are both fast to acquire and help the diagnosis. At the beginning of this century, Mercury et al described a short protocol (less than 30 minutes) designed
to assess the lower limbs with axial T1WI. This can be preformed on children as young as 4 years old, without general anaesthesia.(5)

Depending on the size of the child and available coil, the whole body or sections of the body can be imaged. Mercury et al (5) have shown that imaging of the lower limb alone can guide the diagnosis, as the changes are more easily appreciated at the level of the mid-upper thigh and calves as the muscle bulk is greater and thus early changes are more easily detected. However, several authors believe that the scan should include the shoulder girdle and the pelvic girdle, as well as the lower limbs in their entirety.

The axial slice thickness should be 5-7 mm and the inter-slice gap of 20-50mm, depending on the child size. (2,3) Coronal imaging can also be useful and allows whole body imaging in smaller children.

At our institution we use a whole body MRI protocol, which consists of morphologic T1 turbo spin echo sequences, as well as fat suppressed sequences (STIR) both on axial plane.

T1WI: Allows the best anatomical muscle depiction with identification of muscle shape, volume and architecture, as well as the identification of fatty infiltration.

T2 WI: Demonstrates inflammatory changes, such as muscle oedema.

STIR: Demonstrates inflammatory changes, such as muscle oedema.

Fig. 1: STIR axial image through the shoulder girdle showing marked oedema of the subscapularis muscle

References: Department of Radiology, Centro Hospitalar Lisboa Central, Lisbon / Portugal 2015
Fig. 2: T1 axial image through the shoulder girdle at same level as T2 image depicted on Fig.1. Shows no significant fatty atrophy of the subscapularis muscle.

References: Department of Radiology, Centro Hospitalar Lisboa Central, Lisbon / Portugal 2015

MRI is a standardise approach and degree of change can be graded according to the findings. Fischer et al (4) proposed the grading explained in table 1, which is dependent on the degree of muscle fatty infiltration.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal appearance</td>
</tr>
</tbody>
</table>

1 (Mild involvement)  
Traces of increased signal intensity on the T1WI MR sequences

2 (Moderate involvement)  
Hyperintensity on T1WI with beginning of confluence in <50% of the muscle

3 (Severe involvement)  
Hyperintensity on T1WI with beginning of confluence in >50% of the muscle

4 (End-stage involvement)  
Entire muscle replaced by hyperintense T1WI tissue that corresponds to fat and connective tissue

Table 1: Classification of severity of muscle involvement by Fischer et al (4). The hyperintense areas represent fatty infiltration or connective tissue substitution of the muscle mass.

Such standardized grading allows fast and reproducible assessment of the involvement of each muscle. However, more important than the severity of involvement is the pattern of muscle involvement. These patterns are better seen in individuals with milder forms of disease.

Little is known about the value of contrast enhanced MRI protocols and delayed-enhancement. The use of contrast-enhanced imaging would significantly increase the examination time, but could be beneficial in the detection of early muscle changes, and perfusion studies can perhaps help distinguish between dystrophic and inflammatory changes.(3) On this field further research is needed.

3. Patterns in inherited neuromuscular disease

There is significant clinical overlap in the several patterns of neuromuscular disease and difficulty may arise in distinguishing primary myopathies from neurogenic disorders. Imaging can help in this distinction as patients with primary myopathy present early fatty infiltration of the muscles affected, before significant atrophy ensues.

The most common separation of disease is based on the age of onset and the involvement patterns.(3)
Fig. 3: Differential diagnosis in neuromuscular disease.

**References:** - Beja/PT

i. **Dystrophinopathies** are rare and present with insidious, progressive muscular weakness, with variable rate of progression and age of onset. Becker and Duchenne muscular dystrophy are the most common and have a similar weakness, disability and inheritance (x-linked recessive). Duchenne muscular dystrophy (DMD) is the most severe muscle dystrophy. There is progressive muscle weakness with loss of ambulation. The diagnosis is suspected when muscle biopsy fails to identify dystrophin and is confirmed by genetic screening of the dystrophin gene. A possible differential diagnosis is limb-girdle muscular dystrophy (LGMD) in its sporadic form due to the overlap of muscle involvement as both have muscle hypertrophy either generalized or limited to the calf, with respiratory and cardiac involvement.

MRI of DMD can document progressive muscle involvement. T1WI of young boys may be normal but after the age of 6-7 muscle changes are seen.(2)
Affected muscle groups

Initial fatty infiltration is limited to the gluteus maximus and adductor magnus, with progression to involve the quadriceps, rectus and biceps femoris.

There is marked signal change in the anterior rather than in the posterior thigh muscles.

In the calf, the gastrocnemii present earlier and more severe involvement than other muscles.

Spared muscle groups

There is selective sparing of the sartorius, gracilis, semitendinous and semimembranous

Table 2: Pattern of affected muscles in Duchenne muscle dystrophy.

T2WI/STIR can however depict oedema of muscles that are spared from fatty infiltration. This suggests that muscle inflammation or necrosis is present in early disease before fatty or fibrotic infiltration. In Becker muscular dystrophy the findings are similar to those described for Duchenne muscle dystrophy but less pronounced, in keeping with the less aggressive clinical course.

ii. Limb-girdle muscular dystrophy are an heterogeneous group of illnesses which encompasses proximal muscle weakness affecting the shoulder and pelvic girdle. Most frequently lower limb weakness is noted first. Multiple genetic anomalies have been linked with it, which resulted in a biochemical classification. (2,3)

Affected muscle groups (Fig. 4 and 5)

Minimal involvement: early involvement of the gluteus maximus and the posterior thigh muscles, with predominant involvement of the adductors and semimembranous muscles. The gluteus medius is less involved than the gluteus maximus

Severe involvement with restricted ambulation - marked involvement of posterolateral muscles of the thigh, especially the adductor magnus and biceps femoris, with progression to
the remaining hamstrings and vastus intermedius. Involvement of the vastus medialis and the rectus femoris is observed in patients with advanced disease.

On the leg, there is involvement of soleus and medial head of the gastrocnemius early on in the disease. Involvement of the anterior compartment is only noticed in late disease stages. The tibialis anterior is usually hypertrophied.

Spared muscle groups

Relative sparing of the vastus lateralis, sartorius and gracilis (even in severe disease) On the leg, there is sparing lateral head of the gastrocnemius.

Table 3: Muscle pattern of involvement in Limb-girdle muscle dystrophy

**Fig. 4:** T1 axial image through the thigh, showing atrophy of the adductor muscles (red arrows) in a patient with Limb-girdle muscular dystrophy.

**References:** Department of Radiology, Centro Hospitalar Lisboa Central, Lisbon / Portugal 2015
Fig. 5: T1 axial image through the calves of a patient with Limb-girdle muscular dystrophy, which show no significant change.

References: Department of Radiology, Centro Hospitalar Lisboa Central, Lisbon / Portugal 2015

iii. Dysferlinopathies are characterised by a mutation in the dysferlin gene.

Affected muscle groups
Severe dystrophy of the anterior and posterior thigh compartments is seen

In the leg there is involvement of the posterior compartment

Spared muscle groups
Sparing of the gracilis and satorius

Sparing of the medial head of the gastriconemius

Table 4: Muscle pattern of involvement in dysferlinopathies

iv. Myofibrillar myopathies by myofibrillar degeneration secondary to aberrant desmin aggregation due to mutation in the desmin gene (DES) or in the gene encoding aB-crystallin (CRYAB). MRI is helpful in the diagnosis. Wattjes at al provide in their paper an interesting algorithm to the differential diagnosis of these entities.

Affected muscle groups
In the thigh the semitendinous muscle is the most affected (more than the biceps femoris and semimembranous) The sartorius and gracillis are involved more
frequently and more precociously than other muscles of the thigh.

In the leg the tibialis anterior was involved more than the peroneal muscles.

Table 5: Muscle pattern of involvement in myofibrillar myopathies

v. **Congenital Muscular Dystrophies** (CMD) comprise of a heterogeneous group of diseases, that present early on, during the first months of life, with muscle weakness. The most common form is Ullrich congenital muscular dystrophy. In the muscle affected, the central muscle area appears normal, but there is increased signal at the muscle periphery. This pattern is better visualized in the gastrocnemius, soleus and vasti muscles. An "internal shadow", which can also be seen on US, is present in the rectus femoris.

### Table 6: Muscle pattern of involvement in Ullrich congenital muscular dystrophy.

<table>
<thead>
<tr>
<th>Affected muscle groups</th>
<th>Diffuse involvement of the lateral and posterior thigh compartments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spared muscle groups</td>
<td>Rectus femoris, adductor longus, sartorius and the gracilis</td>
</tr>
</tbody>
</table>

The findings described on table 6 can also be apparent in Bethlem myopathy, which seems to be a milder form of Ullrich CMD, with similar allelic mutations.

In other forms of CMD, such as RSMD1, the anterior and medial compartments are selectively affected, while the posterior and lateral muscles are spared.

vi. **Congenital myopathies** correspond the yet another group of genetically heterogeneous disorders, where muscle weakness tends not to be progressive. The presentation occurs at birth or during infancy. These entities are classified according to the mostly affected muscular structure.(1-3)

### Table 6: Muscle pattern of involvement in congenital myopathies.

<table>
<thead>
<tr>
<th>Affected muscle groups</th>
<th>Gluteus maximus, medial thigh compartment (adductor magnus) and vastii muscles (lateralis and intermedius, in the anterior thigh compartment) In the leg, the soleus, the lateral head of the gastrocnemius and the peroneal muscles are markedly involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spared muscle groups</td>
<td>Rectus femoris, adductor longus and the posterior compartment of the thigh</td>
</tr>
</tbody>
</table>
In the leg, the medial head of the gastrocnemius as well as the anterior muscle compartment are less affected

Table 7: Muscle pattern of involvement in Central core disease (CCD)

vii. Muscle channelopathies and metabolic myopathies do not present many changes on MRI, no muscle fatty infiltration nor oedema could be detected on whole body MRI.

Images for this section:

Fig. 1: STIR axial image through the shoulder girdle showing marked oedema of the subscapularis muscle
Fig. 2: T1 axial image through the shoulder girdle at same level as T2 image depicted on Fig.1. Shows no significant fatty atrophy of the subscapularis muscle.
Fig. 3: Differential diagnosis in neuromuscular disease.

Fig. 4: T1 axial image through the thigh, showing atrophy of the adductor muscles (red arrows) in a patient with Limb-girdle muscular dystrophy.
Fig. 5: T1 axial image through the calves of a patient with Limb-girdle muscular dystrophy, which show no significant change.
Conclusion

Imaging findings, when combined with clinical findings, aim to decrease the number of differential diagnosis in patients with inherited neuromuscular disease. As such, genetic testing can be more efficiently used to identify a specific condition.

Even though the imaging protocols of these conditions have evolved markedly since the beginning of the century further developments are needed. Diffusion weighted imaging is being studied as another diagnostic aid and contrast enhanced images also need to be studied to ascertain their contribution towards the diagnosis in early disease where muscle atrophy and/or oedema are not yet seen.

References


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(6) Li W, Zheng Y, Zhang W, Wang Z, et al; Progression and variation of fatty infiltration of the thigh muscles in Duchenne muscular dystrophy, a muscle magnetic resonance imaging study; Neuromuscular Distoders; 20015 [online]
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