Quantitative MRI in muscular dystrophy

An indispensable trial endpoint?

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In recent years, research into several different therapy approaches for Duchenne muscular dystrophy (DMD) has advanced to the point of clinical trials. A critical issue in designing trials is the choice of appropriate endpoints. To date, assessments of muscle function (such as 6-minute walk distance) or strength (hand-held or integrated chair myometry) have been proposed as primary endpoints. However, the results of these tests depend on patient motivation and engagement, and can involve the recruitment of multiple muscle groups that are affected to different degrees by the dystrophy. This reduces the power of these measures to discriminate change over the relatively short time scales required in trials of novel therapeutics. A number of neuromuscular research groups have proposed that MRI and magnetic resonance spectroscopy (MRS) may provide sensitive, objective measurements of muscle involvement.[1–4]

In this issue of *Neurology*®, Arpan et al.[5] report the effect of corticosteroid treatment in DMD using MRI and MRS: these data come from the multicenter Imaging DMD study (http://imagingdmd.org). Fifteen boys with DMD (age 5–7 years) who were corticosteroid-naive and 15 who were on corticosteroids were recruited. The researchers measured muscle fat replacement using MRS, acquiring data from the soleus and vastus lateralis muscles: these spectra were also used to measure the T2 relaxation time of muscle water in those 2 muscle groups. Additional T2 measurements by MRI (which measures both water and fat contributions) were made in a wider selection of muscles. The key findings were that corticosteroid-naive boys at baseline showed higher T2 relaxation time and more intramuscular fat than the treated boys. When tracked across 1 year, the increase in intramuscular fat replacement in soleus and vastus lateralis muscles was less in the corticosteroid-treated group. In a different group of 16 corticosteroid-naive boys with DMD (aged 5–9 years), the initiation of corticosteroid therapy in 5 of them led to a detectable decrease in T2 in lower leg muscles by both MRI and MRS compared to the rest of that group.

These results provide the first multicenter assessment of the response of 2 MRI biomarkers (muscle fat fraction and T2 relaxation time) to a therapy known to improve outcome in DMD, albeit the present best-practice therapy. Corticosteroid treatment leads to a highly significant attenuation in the rate of fat fraction increase and a reduction in T2 relaxation time, indicating a slowing of the disease process: this is exactly the signature that we would wish to see in a trial of, say, an antisense oligonucleotide therapy. This study substantially adds to the weight of evidence for magnetic resonance as a biomarker for multicenter trials of new therapy in neuromuscular disease.

Quantitative MRI in dystrophic muscle has been gaining momentum. A number of research groups have quantified the fat replacement of muscle by chemical shift MRI in cross-sectional[4,6] and longitudinal studies.[2,3] The sensitivity of quantitative MRI is demonstrated by the study in limb-girdle muscular dystrophy 2I, which has much slower progression than DMD. In 32 patients across 3 countries, fat fraction measurement by MRI was sensitive to disease progression over a 1-year period, whereas measurements of muscle function and strength were not.[3]

One note of caution in extrapolating from the present study results[5]: we must be careful in the general interpretation of T2 relaxation times made using imaging in tissue that is partially fat-replaced. In this study and most others, the data are analyzed to produce a single, global T2 relaxation time, so the result contains contributions from both fat and water. The effects of the inflammatory activity that increases water T2, and the fat replacement that contributes to increased global T2, are not separated as in MRS. In the MRI T2 results of the present study, the marked reduction in water T2 in the lower leg muscles, due to corticosteroid treatment across the 6-month period, must outweigh any T2 increase due to increased fat content, meaning that global T2 is reduced (figure 4): this is shown directly for the soleus muscle by MRS T2 (figure e2A). Using the same technique, the same authors (and others) have demonstrated elsewhere that MRI T2 increases markedly over time in DMD due to increasing muscle fat content.[7]

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A rigorous interpretation of T2 measurements in dystrophic muscle has been set out[8] and an analysis method that can separate the T2 contributions of the water and fat in MRI T2 measurements has been published,[1] allowing distinction of inflammation and fat replacement contributions with an imaging method that allows simultaneous assessment of multiple muscle groups, unlike spectroscopy.

Clinicians may be wary of using quantitative MRI because they regard it as more complex than routine T1-weighted imaging. In Europe, the TREAT-NMD consortium has published guidelines for multicenter MRI protocols[9] and presently the MyoMRI Cooperation in Science and Technology (COST) project (http://myo-mri.eu/) brings together clinicians and MRI scientists with expertise in neuromuscular disease to further develop protocol harmonization. Quantitative MRI does not have to be difficult, but an understanding of the difference between standard radiologic and quantitative protocols is critical.

Clinicians may also be wary of the acquisition time and cost of scanning young children with DMD. Recently, a reduction in acquisition time by a factor of 5, to less than 1 minute per imaging volume, has been validated in MRI fat-fraction measurements in Becker muscular dystrophy[10] using novel acceleration techniques (combined compressed sensing and parallel imaging): such developments in magnetic resonance protocols, when coupled with the results of large multicenter longitudinal studies in muscular dystrophy,[3,5] point the way to making quantitative MRI an indispensable endpoint in clinical trials.

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