MRI of Tibialis Anterior as "Surrogate Measure" in Myotonic Dystrophy Type 1

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Myotonic dystrophy (DM), a dominantly inherited chronic progressive disease, is the most common cause of muscular dystrophy in adults, affecting 1 in 8.000 individuals worldwide.

Myotonic dystrophy DM1 (DM type 1) is due to a CTG expansion in the 3' untranslated region of the DMPK gene and typically involves the distal muscles and those of the face, neck and fingers. In DM2 (DM type 2), due to a CCTG expansion in the first intron of the ZFN9, the proximal muscles are more often involved at onset, particularly in the pelvic girdle. As the disease progresses, the pattern of muscle involvement tend to overlap in the two forms of myotonic dystrophy (DM), with weakness also becoming proximal in DM1 and distal in DM2[1].

Myotonic dystrophy is characterized by a variety of multisystemic features other than muscular (myotonia and muscular dystrophy), including dilated cardiomyopathy, cardiac conduction defects, cataracts, cerebral involvement, insulin resistance and disease-specific serological abnormalities. Clinical manifestations are highly variable and can range from mild to severe wasting of facial and distal limb muscles. In DM1 there is also the severe congenital form of the disease[2]. DM1 and DM2 are caused by the accumulation of expanded CUG/CCUG containing mutant transcripts in discrete nuclear RNA foci in different tissues, including muscle. The toxic mutant RNA triggers a toxic gain of function, leading to aberrant splicing of pre-mRNA and cell dysfunction. In particular, the mutant toxic-RNA alters the level of RNA-binding nuclear regulatory proteins (MBNL1- muscleblind like 1) and CUGBP1 (CUG-binding protein 1) and leads to altered splicing function normally regulated by these RNA-binding proteins which become sequestered within the nucleus. The recently discovered mechanisms underlying these RNA disorders are compatible with the widespread features of DM[3].

The most common form of DM is DM1 and as the disease progresses, some patients develop difficulties walking and experience repeated falls[4]. Foot drop is the term commonly used to describe the type of weakness that typically occurs and contributes to the falls and ankle fractures in these patients[5].

Outcome measures are tests or scales designed to evaluate a particular clinical manifestation that is expected to change as a result of a trial or intervention. These measures should serve as reliable clinical tools to monitor whether a treatment is having an effect. Outcome measures must be reproducible (with both test-retest and inter-rater reliability), valid, responsive to the changes expected to occur in the chosen interval of time of the study and clinically meaningful to patients. Questions to be resolved for DM include: a) which outcome measures are most appropriate for assessment and efficacy; b) which cohorts are most suited for the use of specific outcome measures; and, c) which stage of disease is most appropriate for a given outcome measure for a specific study design. Strength measurements, muscle mass, and functional measures (e.g. the six-minute walk test, 6MWT) may be the most appropriate surrogate end-points measures for certain study designs.

There is nonetheless a need to develop and identify surrogate end point measures that are the most sensitive and reproducible and are the most clinically meaningful to patients in different stages of disease progression in DM1 and DM2. Quantitative myometry using a fixed myometer has good test-retest reliability in DM1. But, it is relatively expensive both in term of the cost of the apparatus and the expense involved for personnel and the time required. Quantitative myometry has other limitations, including patient tolerability, training of personnel and limited responsivity of certain muscles to this method of testing. Manual Muscle Testing (MMT) requires thorough inter-rater training to ensure reliability and requires the necessary time to accomplish this goal. However, MMT costs less and reliability can be improved with repeated, serial training sessions for evaluators. For muscle mass assessment, the Dexa scan has a reasonable cost and has very good test-retest reliability. Outcome measures that rely on muscle strength measurements do have drawbacks. It is often unknown which muscles are most likely to respond to a new therapy. There is day-to-day variability. There are other confounding factors, such as the order of testing different muscles which may contribute to variation. Depending upon the duration of treatment of a group of patients their disease progression may be too slow to show improvement in a clinical trial.

Magnetic Resonance Imaging (MRI) is becoming the method of choice to assess dystrophic muscular diseases. In particular it can be used to establish the underlying pathology and mode of evolution of processes that characterize such diseases, i.e. fibroadipose muscle infiltration and intramuscular oedema- like changes. Although MRI studies are potentially useful to follow the natural history of muscle impairment in DM1, there are no studies in the literature to establish their value. The study by Chantal Coté et al[6] in a large cohort of DM1 (41 patients) describes MRI abnormalities in the tibialis anterior in 80% of the patients and the findings range from oedema-like abnormalities alone to severe atrophy. These abnormalities are helpful to detect and emphasize the sensitivity and strength of MRI to monitor the natural history of DM1. The MRI imaging described in the study by Chantal Coté et al needs to be compared to specific histopathological alterations found in muscle biopsies from the specific portion of the tibialis anterior muscle investigated.[6] The tibialis anterior is one of the selectively involved muscle groups in DM1. The histopathological and molecular abnormalities, such as specific defects in splicing of pre-mRNA, need to be correlated with the alterations observed on MRI study of that muscle. It is probable that the MRI techniques described by Chantal Coté et al will help to identify: 1) asymptomatic or patients with only minimal clinical abnormalities; 2) information that clarifies the natural history and prognosis of the disease;

and, 3) a pharmacological action in this muscle group[7]. Finally, another advantage that the MRI study provides is its ability to assess each individual muscle group and demonstrate subtle changes in muscle structure.

Further studies are necessary to establish MRI studies in specific muscles, such as the tibialis anterior, as a reliable surrogate marker of disease progression and to prove its value in characterizing the severity of DM. Studies are needed to show that MRI as "surrogate measure" reveals certain changes that correlate with CTG repeat size in tissue samples from the muscle examined with MRI[8] and that it also correlates with specific histopathological and splicing defects observed in muscle samples. Such studies can be initiated by comparing results obtained from serial needle biopsy analyses of the tibialis anterior muscle (which allows several biopsies over time) to serial observation on MRI of changes in that same muscle in the same DM patients.

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