DEVELOPMENT OF MAGNETIC RESONANCE IMAGING AS AN ENDPOINT IN MYOTONIC DYSTROPHY TYPE 1

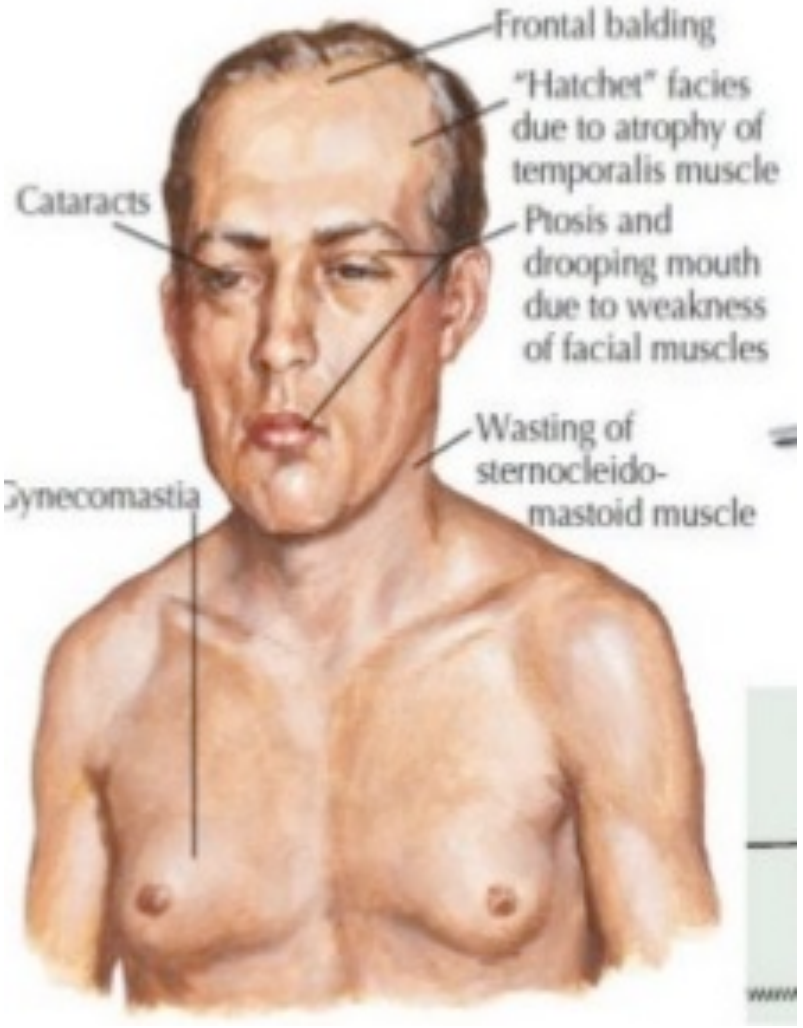
Donovan Lott, PT, PhD, CSCS
University of Florida

Myotonic Dystrophy Type 1 (DM1)

- Myotonic Dystrophy Type 1 (DM1) is the most common form of muscular dystrophy in adults.
- Prevalence is 5-10 per 100,000 worldwide. (Musova; Udd)
- Severity of the disease generally correlates with the extent of CTG repeats. (Klein)
- There is currently no cure for this multi-systemic disease.

Effects of DM1

- Cognitive impairments
- Cataracts
- Smooth muscle involvement
- Progressive muscle weakness & wasting
- Myotonia
- Multiple other systemic symptoms
- Premature death



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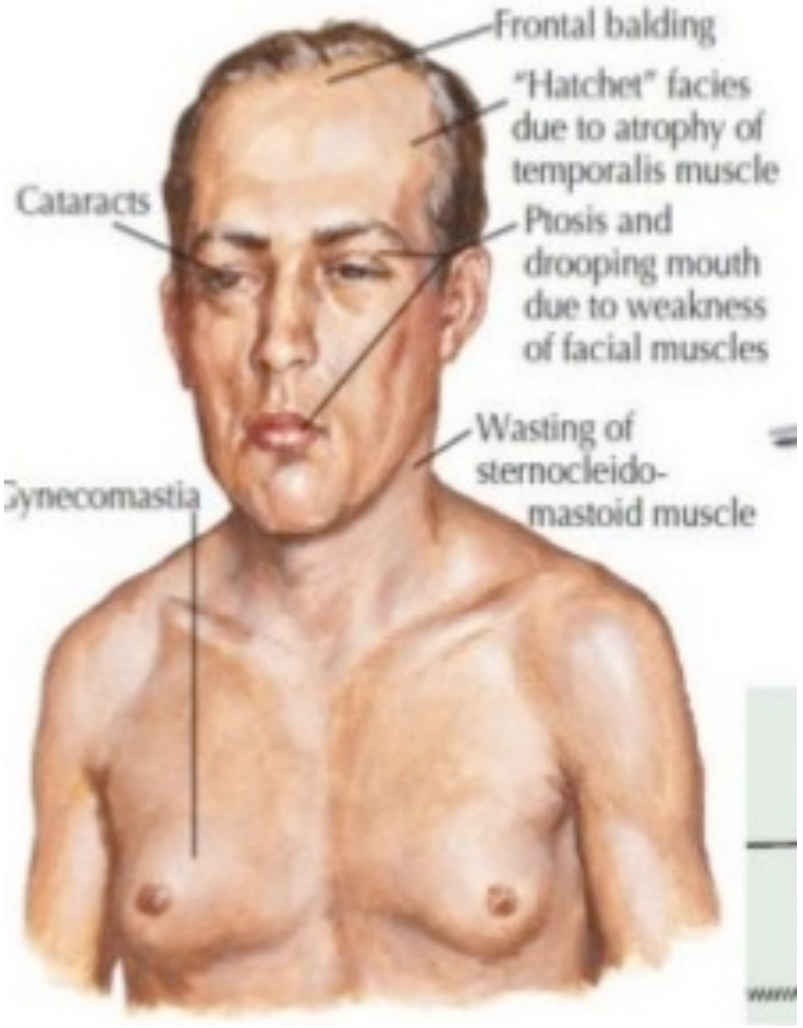
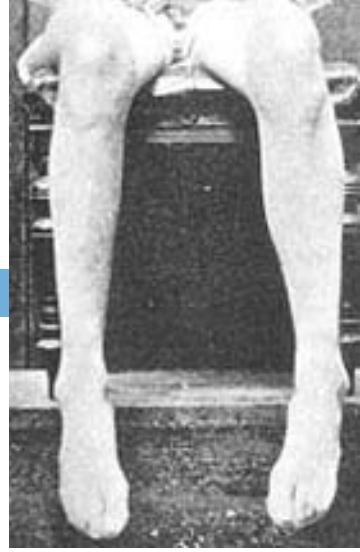


Impact of DM1



Skeletal Muscle Weakness and Atrophy

- Weakness of the lower extremity muscles leads to functional consequences
- Gait and balance disorders (Galli; Missaoui; Hammaren)
- Altered gait mechanics & increased difficulty with walking (Galli; Wright; Hammaren; Moreno)
- Walk at ~half the speed and only take ~50% of daily steps (Wiles)
- Greater incidence of falls: 10 times greater risk for stumbling or falling (Hammaren; Wiles)

Impact of DM1

- Myotonia: Difficulty/inability to relax a muscle after a forceful contraction (Pandya)
- Can be present in the muscles of the leg, jaw, tongue, and distal upper extremity (Pandya; Turner; Udd)
- Impedes finer motor coordination and functional use of the upper extremity (Sugie; Hughes)


Difficulty in releasing grasp

Impact of DM1: FDA meeting 9/15/16

- Symptoms that most affect daily QoL?
  - GI = 16%
  - ***Mobility = 14%***
  - Mental = 13%
  - ***Myotonia***, fatigue, and sleep = ***11%***

- Most important activity impacted by DM1?
  - ***Being active (i.e. exercising) = 25%***
  - ***Being able to asc/descend stairs = 21%***
  - ***Opening doors, drawers, and bottles = 17%***

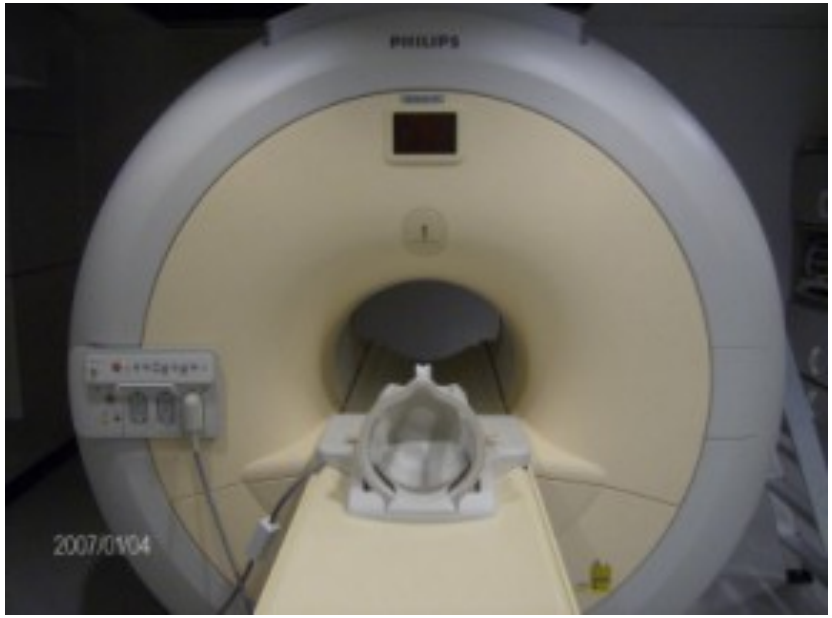
Clinical Trials

- Clinical trials are needed to investigate how new therapeutics can affect muscle, strength, & myotonia.
- Only 1 clinical trial in DM1 (Ionis).
- Validated clinical endpoints as outcome measures for these trials are lacking.
- Repeatable, quantitative, non-invasive endpoints that are sensitive to assessing muscle pathology will be paramount to future clinical trials.

Magnetic Resonance Imaging (MRI)

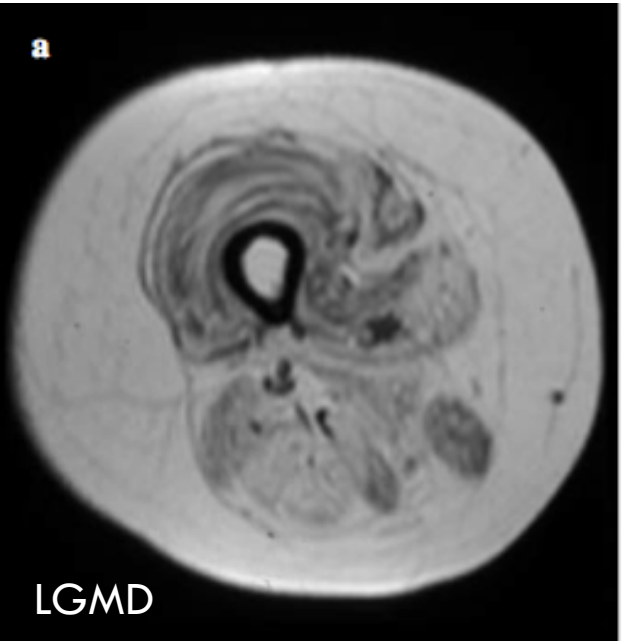
Why MRI???

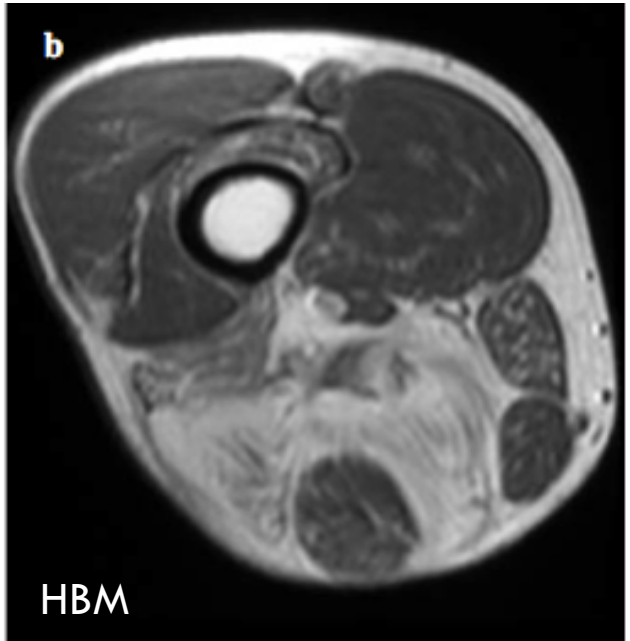
- Noninvasive/nondestructive
- Detailed information
- Quantitative
- Sensitive

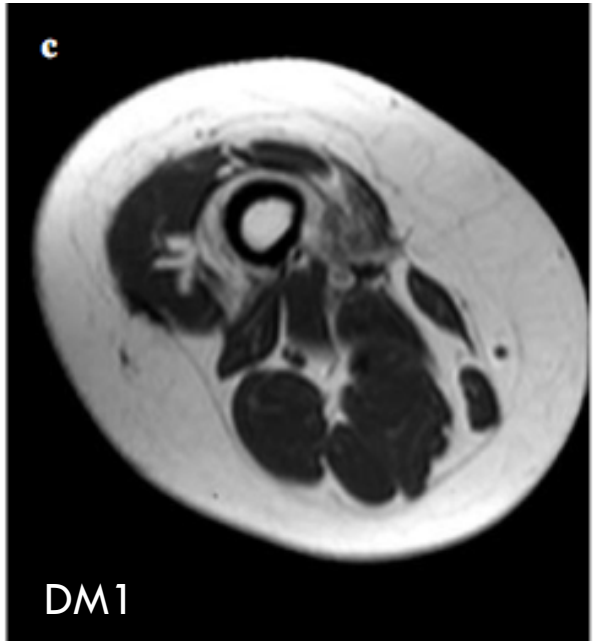


MRI: Preliminary work in DM1 - LEs

- MRI preliminarily evaluation of leg muscles in DM1:
  - Differ from those with other neuromuscular diseases (Stramare)
  - Relate to foot drop (Hamaro)
  - Correlate with strength (Cote; Hiba)

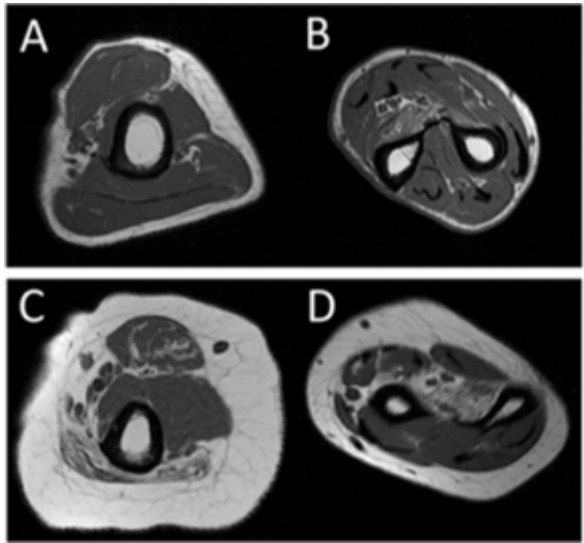






MRI: Preliminary work in DM1 - UEs

- Only two studies have explored the use of MRI in the upper extremities:
  - Muscle involvement of the upper extremity correlated with strength, disease duration, and number of CTG repeats. (Sugie)
  - Hayashi found MRI findings:
    - Correlated with muscle strength and disease duration
    - Did not correlate with CTG repeats



MRI: Preliminary work in DM1

- Provides support for further investigation into how MRI can be used as a clinically relevant endpoint.

- Much more detailed work is needed to determine how MRI can be best utilized as a clinically meaningful endpoint for DM1 in support of the development of new therapies.

ImagingDMD

PI: Krista Vandenborne

- Multi-site study focused on the development of MRI/MRS as a biomarker in Duchenne muscular dystrophy.
- MRI/MRS from both the lower and (more recently) upper extremities.
- Correlations with clinical measures.
- Sensitivity to detect effect of corticosteroids after 3 mo. (Arpan)
- MR biomarkers detect subclinical disease progression. (Willcocks)
- Methodology being used in clinical trials with one of those trials using MRI as its primary outcome measure.

Preliminary work

Pilot Data: Subjects

- MRI data collected for one visit on 12/21 adult subjects with DM1 who were participating in the DMCRN natural history study that had not originally included MR measures.
- MRI data collected day before DMCRN testing.
  - 8 men, 4 women
  - Height: 1.72 (0.08) m
  - Weight: 80.0 (12.6) kg

Pilot Data: MRI data collection

- Philips Achieva 3T whole body scanner
- MRI scans for both lower legs and right upper leg included:
  - T_1-weighted 3D gradient echo images
    - Cross-sectional area; Contractile area
  - T_2-weighted spin echo images
    - T_2 as construct of pathology/inflammation
  - 3-Point Dixon images
    - Fat fraction (FF)

Pilot Data: DMCRN Strength Testing

- Quantitative Muscle Testing (QMT)

- Manual Muscle Testing (MMT)

Pilot Data: DMCRN Functional Testing

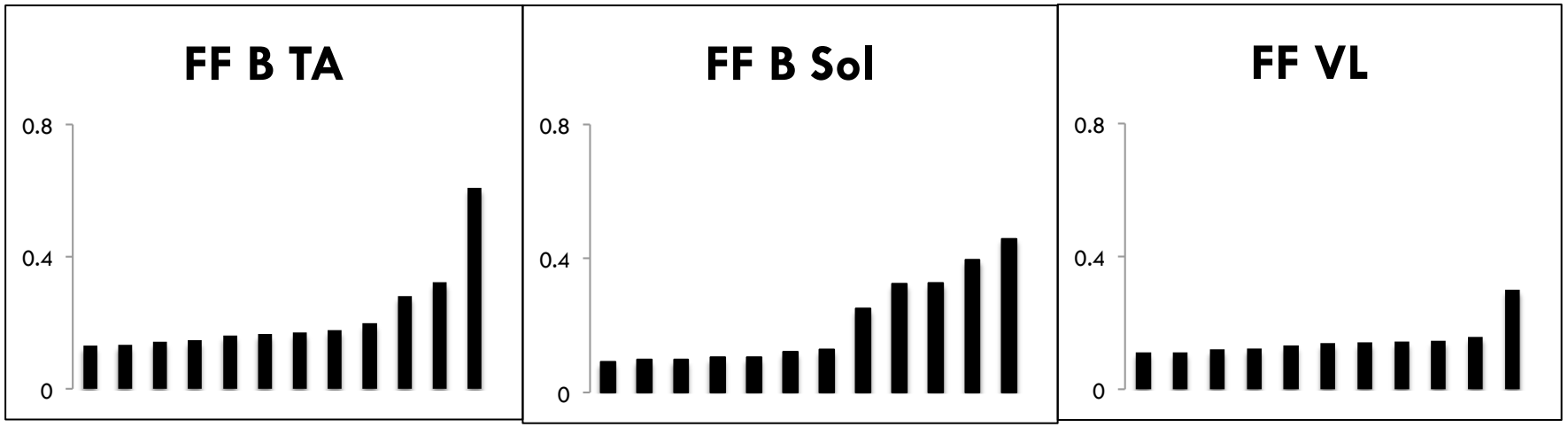
- 30’ Go
- 6MWT
- Time to asc/descend 4 steps

Pilot Data: Functional Testing

- 30’ Go
- 6MWT
- Time to asc/descend 4 steps
- TUG
- 5x Sit<>Stand

Pilot Data: Results

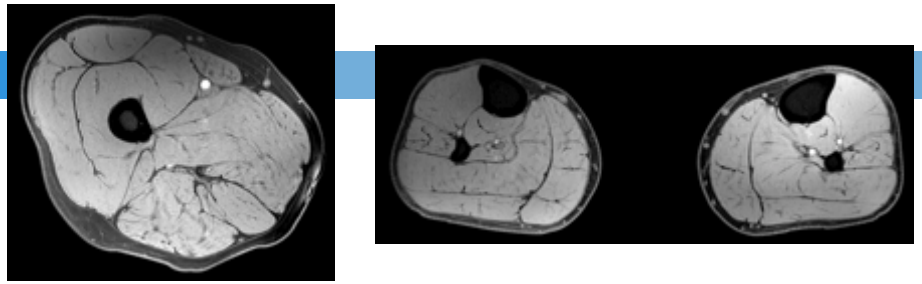
Pilot Data: Results



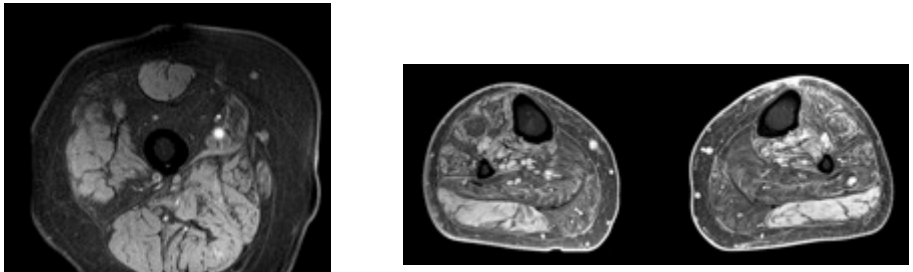
Fat Fraction (FF) quantified from 3-Point Dixon MRI of the bilateral tibialis anterior (B TA) muscles, the bilateral soleus (B Sol) muscles, and the vastus lateralis (VL) muscle for individual patients with DM1.

3D Gradient Echo Fat Suppressed Images of right thigh & both lower legs

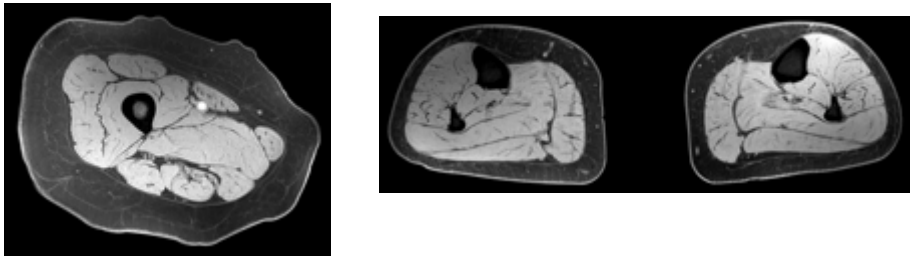
Upper Leg Lower Legs



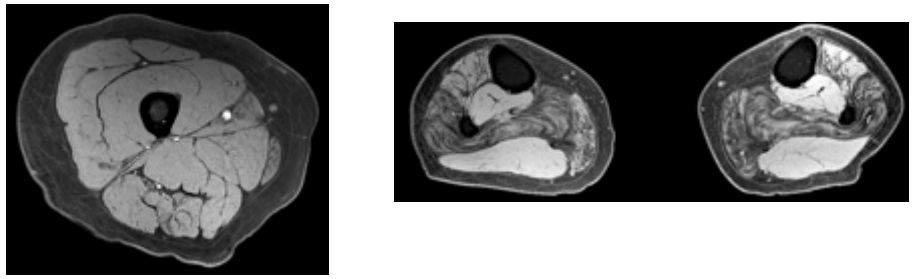
DM1 participant with very little muscle pathology visible.



DM1 participant with extensive muscle pathology present.

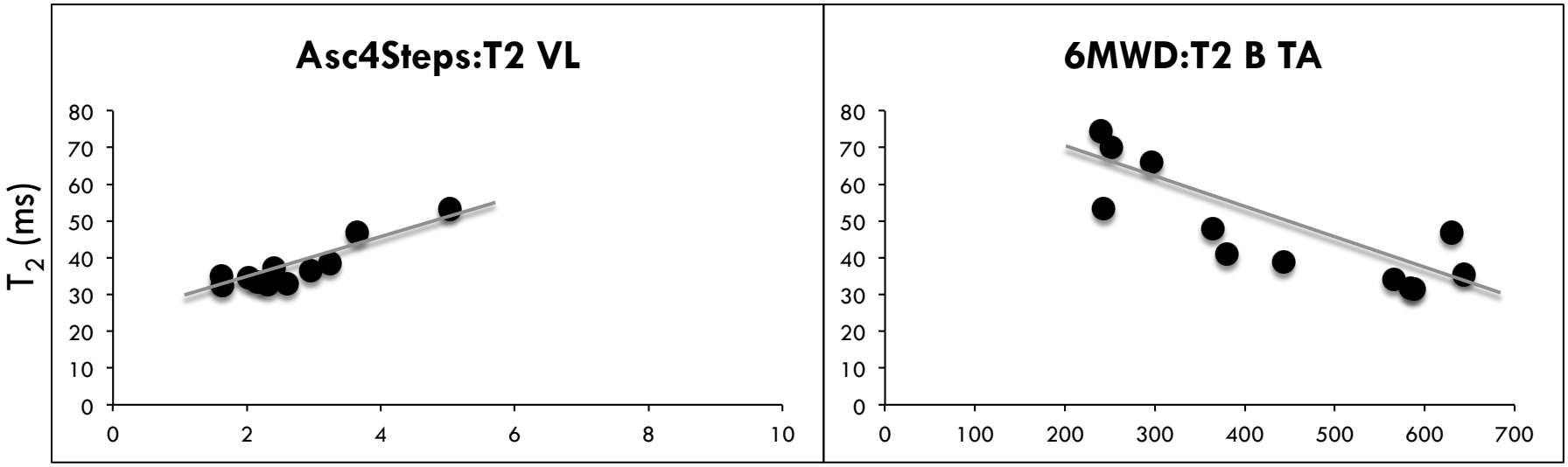


DM1 participant with little intramuscular Pathology evident; however, note the extensive atrophy in both the upper leg and lower legs.



DM1 participant who exhibits moderate-severe muscle pathology in the lower legs but very little in the upper leg.

Pilot Data: Results



Correlations for functional tests with T_2 weighted MRI measures for individuals with DM1: time to ascend 4 steps (s) with T_2 (ms) of the vastus lateralis (VL) on the left ($r = 0.92$) and distance walked in 6 minutes (m) with T_2 (ms) of the bilateral tibialis anterior (B TA) on the right ($r = -0.82$).

MDF RFA

- Development of Endpoints to Assess Efficacy of New Therapeutics for Myotonic Dystrophy

- *"MDF recognizes an urgent need to develop or refine clinically meaningful endpoints in support of the development of new therapies for myotonic dystrophy."*

MDF RFA

- Development of Magnetic Resonance Imaging as an Endpoint in Myotonic Dystrophy Type 1

Overall Objective and Aims

- The overall goal of this proposal is to develop the use of magnetic resonance imaging (MRI) as a clinically meaningful endpoint in people with DM1 that can be used in future clinical trials investigating new therapies for this patient population.

- Aim 1: To evaluate disease involvement in patients with DM1 using quantitative MRI measures of the lower extremity muscles.

- Aim 2: To assess MRI in the upper extremity of patients with DM1 as an endpoint/biomarker.

Subjects

- 25 adult subjects with DM1 (18-55 yrs)
- Onset of DM1 after 10 yrs of age
- BMI $\leq$ 33 kg/m^2
- Able to walk 9m with or without device

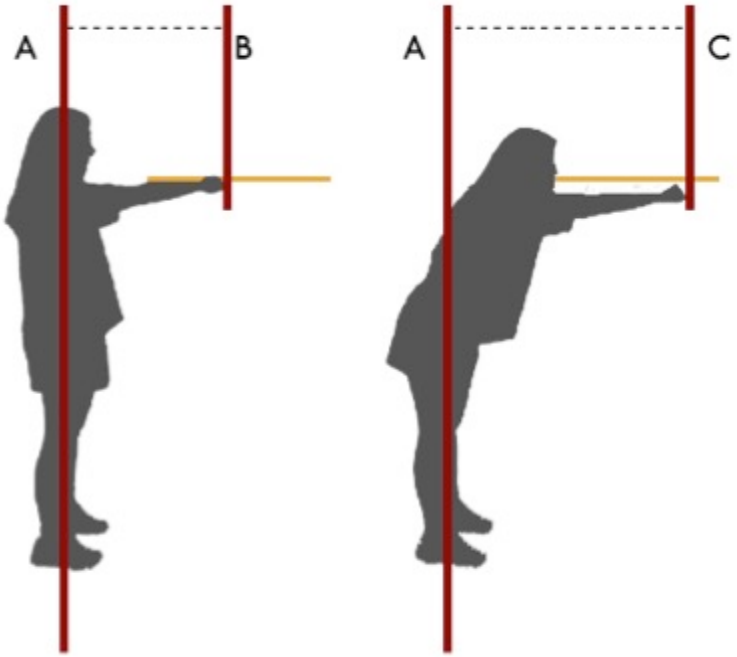
Methods

- MRI scans of both lower legs, right thigh, and right arm to measure quantitative variables:
  - 3D T_1-weighted MRI
    - CSAmax & Contractile area
  - Multi-slice T_2 Spin Echo images
    - Mean T_2 and FWHM of its distribution
  - 2D Multi-slice 8 Point Dixon images
    - Fat Fraction

Methods

- Clinical Tests:
  - Strength with QMT and MMT
  - Walking/mobility with 9m, 4 stair
  - Balance with:
    - Berg Balance Test
    - Functional Reach
  - Myotonia with Grip Relaxation Tir
  - Gait with videography and spatic of gait

Sitting to standing
Standing unsupported
Sitting unsupported
Standing to sitting
Transfers
Standing with eyes closed



Interpreta

Methods

- Questionnaires:
  - Balance/Falls
    - Activities-Specific Balance Confidence (ABC) Scale
    - Ask number of times fallen in past week, month, year
  - Upper Extremity Functional Index
  - Myotonic Dystrophy Health Index

Schedule

Proposed Schedule and Order of Testing		
8:15-9:00 am	Obtain Informed Consent, Review of Eligibility Criteria, MRI Screening, Pregnancy test for female participants	Completed at the McKnight Brain Institute
9:00-11:00am	MRI of legs and arm	Completed at the McKnight Brain Institute
11:15am-11:30am	Vital signs	Completed at the Clinical Research Center
11:30am-12:30pm	Clinical tests for strength, walking, and balance	Completed at the Clinical Research Center
12:30-1:00pm	Lunch	
1:00-1:30pm	Questionnaires regarding falls and Myotonic Health Disability Index	Completed at the Clinical Research Center
1:30-2:30pm	Clinical tests for myotonia in the hand	Completed at the Clinical Research Center
2:45-3:00pm	Clinical gait analysis testing	Completed at the College of Public Health and Health Professions Research Complex

Statistical Analyses

- Examine the relationships between MRI variables of the legs with strength, walking, and balance variables.
- Correlational analyses will also be done for the same MRI variables in the arm with tests for strength and myotonia.
- Based upon MRI variables, receiver operating characteristic (ROC) curves will be determined for discriminating a threshold for people with DM1 who: fall, have a fear of falling that impedes their participation in activities of daily living, have a gait deviation of foot drop, exhibit myotonia, and are limited in using their hand/arm for performing activities of daily living.

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