Modeling Duchenne Muscular Dystrophy Disease Progression: A Longitudinal Multicenter MRI Study

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Introduction: Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease due to a gene mutation that results in the absence of functional dystrophin.[1,2] Currently, there is no cure for DMD but promising therapies have been identified. There is a pressing need for improved biomarkers that are sensitive to disease progression, non-invasive, and can readily be deployed at multiple sites to facilitate rapid testing of new therapies. Magnetic resonance imaging (MRI) and spectroscopy (MRS) offer significant promise in this regard.[3-7] Each is non-invasive, widely available, and can be used to characterize skeletal muscle with excellent precision and sensitivity for detection of DMD muscle pathology. The goals of this study were: 1) investigate DMD disease progression in the lower extremity muscles using MRI/MRS biomarkers, 2) characterize patterns of muscle involvement in upper and lower leg, and 3) summarize DMD muscle progression using a simple and robust modeling approach.

Methods: Data were acquired from 128 DMD boys and 31 healthy control boys using 3T MRI instruments at three institutions. The DMD boys were followed at intervals ranging from 3 to 12 months for up to three years. ^{1}H MRS data were acquired using a single voxel spectroscopy sequence[8] to estimate fat fraction (FF) in vastus lateralis (VL) and soleus (Sol) muscles. MRI quantitative T_2 (qT_2) values were determined using a 2D multi-slice multiple spin echo (N=16; 20 ms ≤ TE ≤ 320 ms) sequence in the upper and lower leg, and analyzed for eight muscle groups. Longitudinal changes in FF and qT_2 (response measures) were estimated at the group and individual levels using non-linear mixed effects (NLME) modeling. The fitting kernel included a 3-parameter continuous distribution function (CDF; the integral of a normalized Gaussian function and shows a sigmoidal time dependence) parameterized by: **i)** the maximum expectation value of the response measure; **ii)** the age at which the response measure change is half its maximum value; and **iii)** a progression time constant.

Results: MRS FF and MRI qT_2 values of all muscle groups were significantly elevated in DMD compared to control boys. Both MRS FF and MRI qT_2 increased significantly with time in DMD with the average annual rate of increase varying substantially with age and between muscle groups; with upper leg muscles showing the greatest overall change and lower leg muscles of tibialis posterior and anterior showing the smallest change. The effect size (Cohen's *d*) for annual change in FF for boys with DMD was age dependent and ranged from ~0.2 to ~2 in young (5-6.9 y) and older boys (9-10.9 y), respectively. To quantify this behavior we applied non-linear models at the group and individual levels. **Figure 1** shows the longitudinal MRS FF changes for a boy with DMD (triangles=VL; squares=Sol), and CDF model result (solid lines). **Figure 2** shows the aggregate group longitudinal MRS FF data for VL and Sol with NLME model results overlaid as solid lines. NLME modeling revealed that the maximum rate constant for FF increase was 60% greater for VL than Sol ($P<10^{-5}$) and occurred at an earlier time in VL [10.9 (±1.6) y] compared to Sol [14.6 (±3.0) y, $P< 10^{-6}$]. **Figure 3** plots the modeling results for MRI qT_2 for 3 upper leg muscles and 5 lower leg muscles (a non-zero constant was included in the CDF kernel to account for the initial T_2 value; Fig 3 ordinate units are ms). Overall findings show that upper leg progression > lower leg progression, with biceps femoris and VL showing greatest involvement at earliest times whereas the anterior and posterior tibialis are relatively preserved. Gastrocnemius, Sol, and peroneus demonstrate intermediate progression and are nearly super-imposable (Fig 3) with respect to group average T_2 progression. NLME modeling returned very similar results for MRS FF and MRI T_2 measures.

Discussion: Quantitative MRS FF and MRI T_2 values provide sensitive unbiased readouts of DMD disease progression. Group average and individual disease trajectories across multiple muscles are efficiently summarized by NLME modeling of longitudinal MRS FF or MRI qT_2 data. The non-linear CDF model captures the slow initial rise, fast midterm progression, and the late term tapering of muscle FF and qT_2 change observed in longitudinal DMD data. The derivative of the CDF is a Gaussian function that provides an estimate of the instantaneous change in FF or qT_2 and hence disease progression. Mechanical injury may be highly detrimental to dystrophin lacking muscle cells as these cells more quickly exhaust their finite number of injury/repair cycles before cell death and fat infiltration. The observed sigmoidal behavior for muscle FF and qT_2 increase likely reflects the probabilistic nature of disease progression that depends on two substrates; the average number of injury/repair cycles experienced by muscle cells, and the number of viable muscle cells that remain in the tissue region of interest. In early term, the slow initial FF or qT_2 rise may reflect a phase in which muscle still has substantial regenerative capacity. The midterm progression is increased because a high fraction of muscle cells are at or near the injury/repair limit and there also are many cells remaining that can die and be replaced by fat. In late term there is little muscle remaining to be replaced by fat, hence the absolute change in fat (or muscle lost) at this stage is low. Taken together, the approach described provides a powerful method to track disease progression and therapeutic interventions in DMD.

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