Diffusion tensor imaging of muscle degeneration in a mouse model of ALS

J. Zhang[1], G. Zhang[2], S. Mori[1], and K. A. Sheikh[2]

[1]Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that causes progressive degeneration of the motor neuron system. Progressive muscle atrophy, in response to denervation, is one of the markers of disease progression in ALS. Muscle atrophy is the result of gradual reduction in muscle fiber caliber after denervation. Transgenic mice that carry SOD[1] mutations have been widely used for pre-clinical testing and development of therapeutic treatments. There are several ways to detect muscle denervation. Previous MR studies have showed that de-nervation enhance muscle tissue T_2 signal[1]. To measure muscle atrophy, i.e., reduction in muscle mass, and reduction in muscle functions, people has relied on behavior test, in vivo or ex vivo MRI, and histology. Diffusion tensor imaging uses water molecule random diffusion to probe tissue microstructures. Previous reports have demonstrated that DTI can be used to study ischemia and denervated skeletal muscles[2]. In this study, we evaluated the effect of denervation on T_2 and DTI measurements in SOD[1] mice, and investigated whether these measurements can be used as potential surrogate markers in detection and evaluation of muscle de-nervation and atrophy.

Methods: In vivo MRIs on SOD[1] and control mice (n = 5 for each group) were performed on an 11.7T MR system from the 10^{th} week to 15^{th} week after birth. For each mouse, six diffusion weighted (DW) images (b = 700 s/mm^2) and one non-diffusion weighted (b = 50 s/mm^2) image were acquired with a multiple spin echo sequence (TEs = 27/37 ms, TR = 1.5 s, NA=2, Δ = 14 ms, δ = 6 ms, resolution = 0.3 x 0.3 x 1.5 mm^3, 10 axial slices, diffusion gradient direction: [0.707, 0.707, 0], [0.707, 0, 0.707], [0, 0.707, 0.707], [-0.707, 0.707, 0], [0.707, 0, -0.707], [0, -0.707, 0.707]). T_2 map were calculated from multiple spin echo images (TR = 6000 ms, TEs = 6.3/12.7/19.0/25.4/31.8/38.0 ms, resolution = 0.3 x 0.3 x 1.5 mm^3). High resolution T_2-weighted images (RARE, TE = 40 ms, TR = 6 s, ETL = 4, NA = 8, resolution = 0.08 x 0.08 x 0.3 mm^3) and T_2*-weighted images (FLASH, TE = 5ms, TR = 100 ms, NA =12, resolution = 0.08 x 0.08 x 0.3 mm^3) were also acquired for muscle volume measurements. Diffusion tensors were calculated using a Log-linear fitting method, and fractional anisotropy (FA), mean diffusivity (MD), axial and radial diffusivity (D_a and D_r, respectively) were also calculated. Mouse lower leg muscles were manually segmented to measure the total muscle volume.

Results: Starting from the 10^{th} week after birth, SOD1 mice started to show muscle atrophy in the lower leg (Fig. 1A). We detected significant reduction in lower leg muscle volumes compared to control mice at the 13^{th} week ($p < 0.05$, Fig. 1B). Muscle T_2 values showed modest increases after the 10^{th} week, and the increases were significant from 11^{th} week to 14^{th} week compared to baseline values. FA measurements did not show apparent change, while MD and D_r showed significant decreases after the 13^{th} week, synchronized with the change in total muscle volumes. Correlation between the total calf muscle volume and radial diffusivity show strong linear correlation (r = 0.8593, r^2=0.7384).

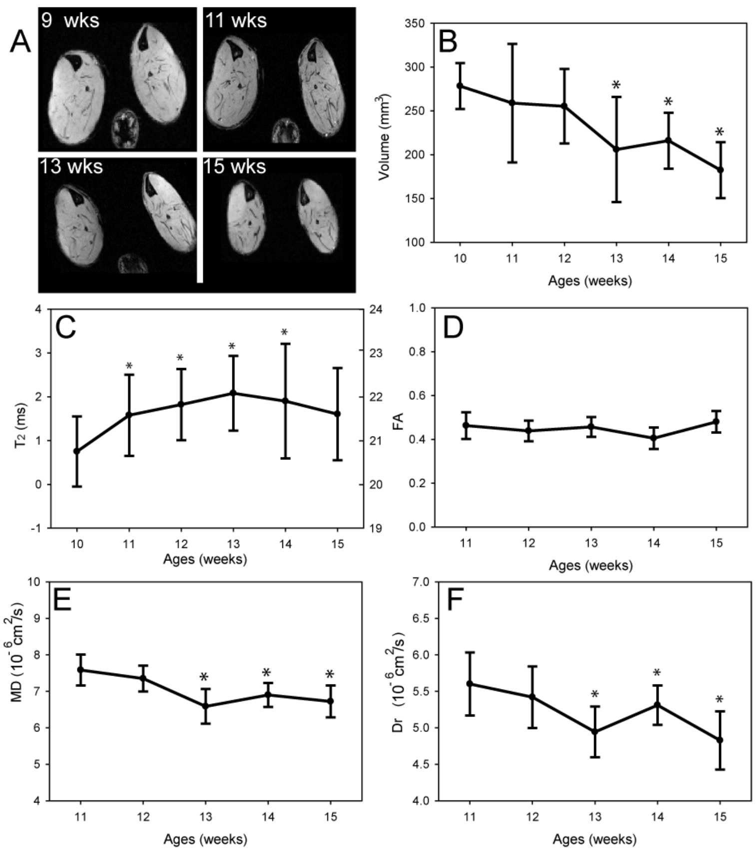

Fig. 1: A: Cross-sectional images of lower legs in a SOD1 mouse at 9, 11, 13 and 15 weeks. B – F: changes in leg muscle volume, muscle T_2, FA, mean diffusivity (MD) and radial diffusivity (Dr) from 10 week to 15 week. Asterisks (*) indicate values are significantly different from values of control mice ($p < 0.05$, t-test).

Discussion and conclusion: The results show that muscle T_2 is a sensitive marker for detecting muscle denervation, well ahead of muscle volume and DTI measurements. The strong correlation between the measured radial diffusivity (D_r) and muscle volume suggests that changes in radial diffusivity may reflect change in mean muscle fiber calibers in denervated skeletal muscles. Compared to conventional volume measurements using structural MRI, which often involves time consuming and operator dependent manual segmentation procedure, DTI may be a efficient alternative approach.

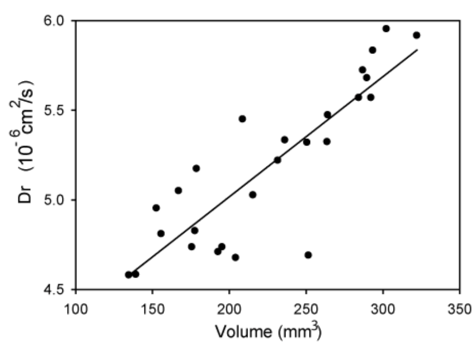

Fig. 2: Correlation between mouse lower leg muscle volume and radial diffusivity (D_r).

References: **1.** Bendszus, M. et al. Neurology, 57 (9) (2002), pp. 1709-11. **2.** Saotome, T. et al. Magnetic Resonance Imaging, 24 (2006), pp. 19-25.