MAGNETIZATION TRANSFER CONTRAST IN MRI AS A DIAGNOSTIC AND MONITORING TOOL FOR MUSCULAR DYSTROPHY

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Introduction: Throughout the progression of dystrophic myopathies, the affected muscle tissues undergo numerous cycles of degeneration and regeneration due to their high susceptibility to injury. Upon exhaustion of the regenerative capacity of these muscles, damaged fibers are progressively replaced by fat and connective tissue. Underlying this elevated vulnerability to damage is a deficiency in dystrophin or dystrophin associated glycoproteins (DAGs). Since the pathological effects are often due to the lack of a single protein, the muscular dystrophies are well suited for gene therapy, stem cell therapy, as well as pharmaceutical treatment. Current methods of monitoring efficacy of therapeutic intervention and diagnosis rely heavily on tissue biopsy and histology. The development of non-invasive imaging modalities is greatly needed to evaluate novel therapeutic approaches in their ability to restore the dystrophin/DAG complex.

Experimental: A total of 25 mdx, 11 C57BL10, 13 sgcg−/−, and 4 sgcα−/− mice were studied. One leg of the sgcα−/− mice was treated by IM injecting neonates with a muscle specific recombinant adeno-associated virus (1x10^11 vg of rAAV2/1-tMCK-sgcα) which expresses the human form of the missing α-sarcoglycan (sgcα). MRI/MRS. Animals were anesthetized using gaseous isoflurane in oxygen. MRIs were acquired with a FOV=1cm, matrix=256x128, slice thickness=1mm, nexe=2 and a TR= 2s. To determine transverse relaxation rates (T2) a spin-echo (SE) diffusion weighted sequence (b=4.2 s/mm^2) was performed at two echo times (TE=14,40ms). Magnetization Transfer (MT) was measured using the same SE sequence as used for T2, except that a single transaxial image slice location was acquired using a MT preparation pulse (400x25 msec square pulses, 6 µT, at offsets of ±20, ±15, ±10, ±5 KHz). All values are reported as mean±SEM and differences between groups were determined using ANOVA and paired t-tests with a level of significance set at p<0.05.

Results and Discussion
Masson’s trichrome staining showed significantly larger amounts of fibrotic tissue in the gastrocnemius (gastroc) muscle of 24 month old mdx mice compared to 28 month C57/Bl10 mice (Fig 1A). Overall the Z spectra obtained from the tibialis anterior (TA) and gastroc muscles of old (>72wk) mdx mice were upwardly shifted compared to that of age matched controls (Fig1B). We further compared MT in old (18-28 month) and young (1-5month) dystrophic and C57 mice at a single offset frequency (Fib 1C). Hyperintense regions (HI) on T2 weighted showed significant MT contrast. The expression of α−sarcoglycan in the young sgcα−/−, resulted in a 27% (p<0.05) decrease in T2 and a 5.4% (p<0.05) change in MTR in the treated vs. the untreated contralateral muscles.

Conclusions: We found significant differences in MT characteristics of healthy and fibrotic dystrophic muscles indicating that MT may provide a noninvasive measure of disease progression and therapeutic intervention for the dystrophies.

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