Quantitative Characterization of Mouse Calf Muscle Degeneration after Left Sciatic Nerve Axotomy with Magnetic Resonance Imaging

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Introduction: Muscles, once denervated, show weakness and progressive atrophy. Clinically, muscle weakness/atrophy is one of the early symptoms of diseases such as ALS. Mouse models are widely used in research on human neuromuscular diseases. In these studies, muscle morphology is an important index to evaluate disease progression and treatment efficacy. In vivo techniques that can examine changes in muscle morphology are of great importance for animal studies. Previous studies demonstrated changes in muscle T_1, T_2 and cross section area after injury of associated nerves (1). However, information on morphological changes of individual muscle after denervation is not available. In this study, we applied high resolution imaging and computational techniques to characterize the progression of muscle atrophy after sciatic nerve transection.

Methods: All procedures were approved by the Animal Research Committee of the Johns Hopkins University, School of Medicine. Six mice (C57BL/6J, male, 10~11 week) were used. Axotomy was performed on the left sciatic nerve in four mice and the rest were used as controls. In vivo images of mouse lower legs were acquired on an 11.7 Tesla NMR system using a fast spin echo (FSE) sequence with twin navigator echoes for motion correction. Imaging parameters are: TR/TE = 18/800 ms, ETL=4, fat saturation enabled, and an resolution of 0.08 mm x 0.08 mm x 0.4 mm. Low resolution images were acquired with a TR/TE1/TE2/TE3 = 800/12/24/36ms, ETL=4, fat saturation enabled, and an imaging resolution of 0.15 mm x 0.15 mm x 0.5 mm. T_2 values of muscle tissue were calculated from the three low resolution images. Baseline images were acquired before the sciatic nerve axotomy. Post surgery images were first acquired at the third day, and then weekly up to the sixth week (total 8 sessions for each mouse). For ex vivo study, animals were sacrificed and images were acquired from fixed samples using 3D FSE, TE/TR=60/2000 ms, ETL=4, and an isotropic resolution of 0.08 mm/pixel.

Ex vivo images of one control mouse was selected as template. A 3D atlas of bones and four muscles (TA: the tibialis anterior, MG: medial gastrocnemious, LG: lateral gastrocnemious, and S: soleus muscle in Fig. 3) in mouse lower legs was created via manually segmentation. Nonlinear transformation between the template and other images were obtained using a nonlinear landmark matching technique (2). The transformations deformed the atlas into each subject image. Minor manual correction was performed to ensure the deformed atlas agreed with subject images. Volumetric measurements of individual muscle were obtained from these deformed atlases. Using the segmentation results and large deformation diffeomorphic metric mapping (LDDMM) (2), local changes in muscle volumes were quantified using the Jacobian of the mapping.

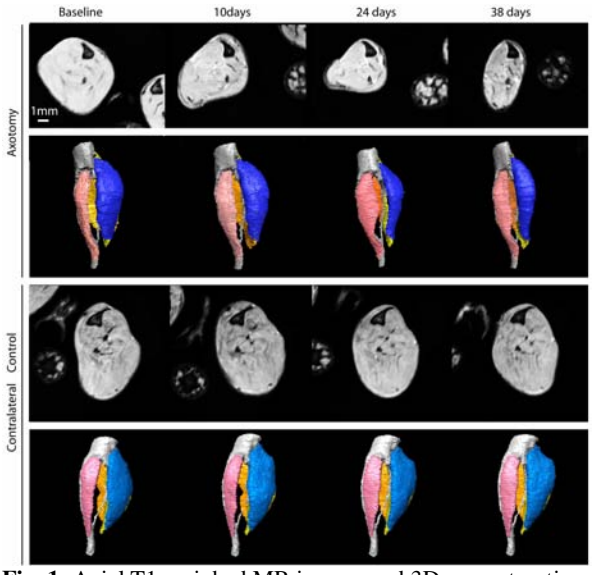

Fig. 1: Axial T1-weighed MR images and 3D reconstruction of mouse calf muscles after axotomy. Top two rows: calf muscles on the left side (with axotomy) in one mouse. Bottom two rows: calf muscle on the right side in the same mouse.

Results: Muscle atrophy on the injured (left) side was first appreciated by visual inspection of the animals around 2 weeks after surgery. In axial MR images, gradual reduction in cross section area of left calf muscle as well as circumference of the calf over time compared to the right side were observed (Fig. 1). The shape of the muscles on the left side changed considerably in consecutive axial images, while the shape of the contralateral muscles remained approximately the same. In Fig. 1, 3D reconstructions of the tibialis anterior (pink), soleus (orange), medical (green) and lateral gastrocnemius (blue) muscles enabled quantification of atrophy of several major muscles. Elevation in muscle T_2 value in denervated muscles was detected at day 3 after axotomy, and remained so during the entire course. No significant difference in the amount of T_2 increase was detected among different muscles.

3D volumetric measurements (Fig. 2) showed that the degree of atrophy was not the same among muscles innervated by the sciatic nerve in mouse lower leg and denervation had greater effect on the gastrocnemious muscles than the tibialis anterior muscle. The gastrocnemious muscles showed the highest degree of atrophy (more than 50%), while the tibialis anterior muscle showed only 25% atrophy. Using LDDMM, spatial pattern of muscle atrophy was revealed by LDDMM, and shown in Fig. 3. Regions that show severe atrophy are in red, while regions with milder atrophy are in green.

In summary, muscle morphology can be studied using high resolution MRI in 3D. With advanced computational techniques, spatial and temporal patterns of morphological changes in individual muscles can be quantified.

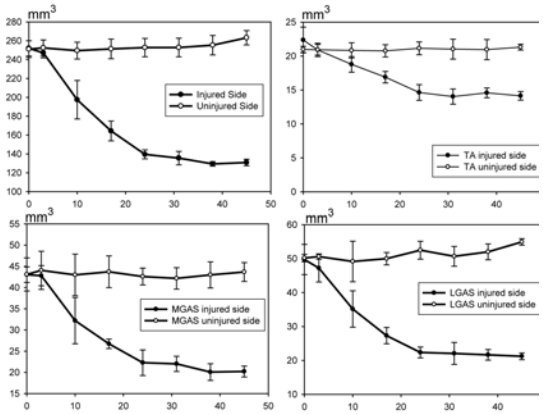

Fig. 2: Volumes of the entire calf (upper left), the tibialis anterior (upper right), the medial and lateral gastrocnemious muscle (lower left and right) on the left (solid dot) and on the right (n=3).

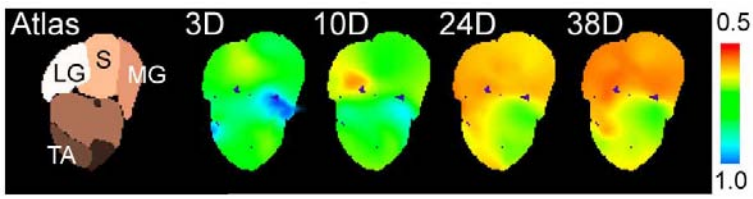

Fig. 3: Muscle atlas and Jacobian maps that show progressive muscle atrophy at 3 days, 10 days, 24 days, 38 days after axotomy. .In the jacobian map, color represents the degree of local atrophy, from normal (blue) to severe atrophy (50% volume decrease, red).

References:

1. Bendszus, M., et al. Neurology, 57(9) (2002), pp.1709-11
2. Miller, M., et al. Annu. Rev. Biomed. Eng. 4 (2002), pp. 375-405