Quantifying Muscle Inflammation with Diffusion Basis Spectrum Imaging

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Purpose: Once considered a tropical disease, infectious myositis is an underappreciated emerging global affliction. Importantly, muscle-tropic viruses often spread to the central nervous system leading to dramatically increased morbidity. There is a clear need for non-invasive biomarkers of disease progression and treatment response in myositis. Diffusion basis spectrum imaging (DBSI) has been previously utilized to separately quantify inflammatory pathology and fiber pathology in white matter diseases such as multiple sclerosis. Structurally, muscle is similar to white matter with an organized and oriented fiber structure. For this reason, attempts have been made to utilize diffusion tensor imaging to characterize muscle pathology including muscle inflammation. We sought to evaluate whether DBSI could detect inflammation-mediated changes in a mouse model of myositis.

Methods: Intracerebral inoculation of Theiler's murine encephalomyelitis virus (TMEV) is commonly used as a model of multiple sclerosis. However, systemic inoculation of TMEV leads to acute myositis (1). 12 day old C57BL/6 mice were inoculated intraperitoneally (IP) with 100 ul containing 6 x 10^6 PFU TMEV (BeAn strain). Mice were euthanized at 15 days post infection. The left hindlimb was dissected and embedded in 2% agarose. MRI was performed in a 4.7 T small-animal Agilent/Varian DirectDrive scanner using a foil solenoid coil with a 15 mm diameter. A multi-echo spin-echo diffusion-weighted sequence with 99 diffusion directions and weightings was employed with maximum b-value of 1500 s/mm^2. The 99 diffusion-encoding directions were selected so that the position vectors are the entire grid points (qx, qy, qz) over the 3-D q-space under the relationship $(qx^2 + qy^2 + qz^2) \leq r^2$, where r = 3. Spin echo T1-weighted (TR = 500 ms, TE = 17ms), magnetization transfer (2 s hard pulse at 2 kHz offset), and T2 maps (TR = 4 s, 12 TEs from 15 to 180 ms) were also acquired. Data was analyzed with DBSI multi-tensor and conventional DTI single-tensor model analysis packages developed in-house with Matlab (2). T2 times were calculated via non-linear fitting to a single exponential. Regions of interest (ROI) were identified in the T1-weighted image and copied onto the parametric maps. At present we have performed DBSI analysis in one control and three TMEV samples. Data is presented as mean for the control and mean ± standard deviation for the three TMEV samples.

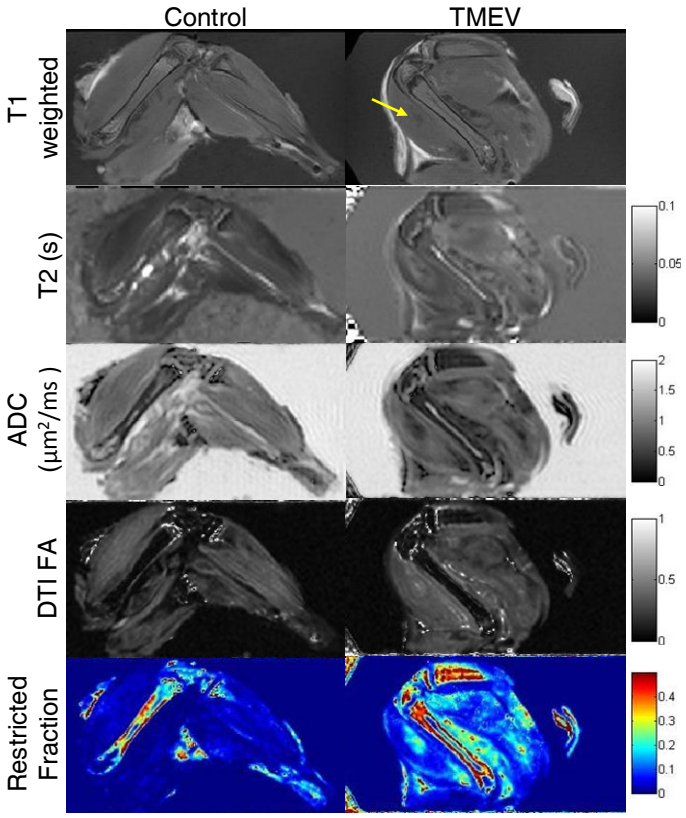

Figure 1. Anatomical T1-weighted image, T2 times and diffusion parametric maps for a representative control and TMEV-infected hindlimb. Yellow arrow indicates one example hypointense lesion in the T1-weighted image.

Results: Figure 1 presents representative anatomical T1-weighted images plus parametric maps of control versus TMEV-infected hindlimbs. TMEV infection of skeletal myofibers induces inflammation and subsequent dystrophic calcification with loss of ambulation in wild type mice. Lesions were identified as hypointense in T1-weighted images (yellow arrow in Figure 1). In comparison to control muscle, T2 times (25 vs. 42 ± 8 ms) increased in the lesion. Similarly, the ADC (0.87 vs. 0.47 ± 0.03 μm^2/ms) is reduced while the DTI-derived FA (0.29 vs. 0.36 ± 0.05) is less affected. With DBSI, we calculated a restricted isotropic diffusion tensor fraction with ADC < 0.3 μm^2/ms which is usually associated with increased immune cell infiltration. Calcification could also be reflected in the restricted fraction in this case. In comparison to the control muscle, the restricted isotropic diffusion tensor fraction is markedly increased (0.02 vs. 0.20 ± 0.03) in the lesion. More interestingly, changes were also observed in the normal-appearing muscle. In comparison to the control muscle, T2 times (25 vs. 40 ± 5 ms), and restricted isotropic diffusion tensor fraction (0.02 vs 0.06 ± 0.02) increased while the ADC (0.88 vs. 0.79 ± 0.04 μm^2/ms) reduced. The DBSI-derived FA was essentially the same (0.29 vs. 0.29 ± 0.01). The MTR was also measured but showed no difference between control (0.79), normal-appearing muscle (0.80 ± 0.01) and lesion (0.79 ± 0.01)

Discussion: The present work is the first example of DBSI being applied to muscle pathology. At first glance, DBSI seems capable of detecting inflammation in the muscle that might be missed by just looking at ADC or FA. However, more samples are needed for definitive results as well as validation with histology. Those experiments are currently ongoing.

Conclusion: DBSI could potentially be used to assess inflammatory pathology in the muscle.

References: 1. Watson, N. & Massa, P. *J Immunol* **192**, 52.21 (2014). 2. Wang, Y. et al. *Brain* **134,** 3587–3598 (2011).