Diffusion-weighted MRI characterization of white matter injury produced by axon-sparing demyelination and contusion spinal cord injury in rats

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BACKGROUND: Recent literature suggests that diffusion-weighted MRI (DW-MRI)/diffusion tensor imaging (DTI) may distinguish pure demyelinating injury (isolated elevation in transverse diffusion) from white matter injury that includes associated axonal damage (decreased longitudinal diffusion)[1-3]. Such distinction would potentially have important diagnostic and prognostic implications. We tested the hypothesis that acute, axon-sparing demyelination in the spinal cord would result in preserved longitudinal and increased transverse diffusion. In addition, we sought to compare diffusion parameters in axon-sparing chemical demyelination to those produced by axon and myelin injurious contusion injury during both acute and chronic time points with histologic and immunohistochemical correlation.

METHODS: 23 adult female Long-Evans rats were used. Animals received either ethidium bromide (EB; n=12) microinjections (chemical demyelination) into the lateral funiculus at C4-C5 and saline (sham) into the contralateral lateral funiculus, or were subjected to unilateral spinal cord injury (SCI) (100kdyn) at C5 using the Infinite Horizons (IH) impactor (n=9). 2 animals served as uninjured controls. MRI (Varian 7T) was performed *in vivo* with respiratory gating at 7-8 days (acute) or ~70 days (chronic) after injury for both injury models. Sequences included spin echo multi-slice T1, T2, and diffusion weighted imaging in the X, Y and Z gradient directions following confirmation of cord alignment with a 3-plane localizer. Directional ADC values were calculated based on the equation $ADCn=\ln[S_0(b_o)/S_n(b_n)]/(b_n-b_0)$. Anisotropy index was derived according to $AI= [ADC(z)-ADC(x)]/[ADC(z)+ADC(x)]$[4].

RESULTS: Compared with sham control, acute EB demyelination results in both a significant elevation in transverse diffusion ($p<0.004$) and significant reduction in longitudinal diffusion ($p=0.01$), despite histological evidence of axon preservation. Alterations in transverse and longitudinal diffusion were not significantly different from those observed with severe acute contusive white matter injury, where histology demonstrates severe combined axonal and myelin injury. The chronic EB lesion demonstrates near complete endogenous remyelination histologically with associated normalization of transverse and longitudinal diffusion values, whereas chronic contusion white matter injury results in persistently elevated transverse and normalized longitudinal diffusion values.

DISCUSSION: To our knowledge, this is the first *in vivo* DW-MRI study of focal, axon-sparing demyelination. In the acute setting, increased transverse and decreased longitudinal diffusion with chemical demyelination is indistinguishable from that seen with acute contusive injury, despite dramatic pathologic differences between injury models. These data suggest that in the acute setting, transverse and longitudinal diffusion values are sensitive, yet non-specific markers of white matter pathology and cannot distinguish acute demyelination from combined acute axon and myelin injury, as seen with contusion. In the chronic setting, persistently elevated transverse diffusion values distinguish chronically contused from remyelinated (chronic EB) white matter.

REFERENCES/ACKNOWLEDGMENTS: Supported by NIH:T32 (EB001631-07), Margulis Society and C.H. Neilsen Foundation (124585).

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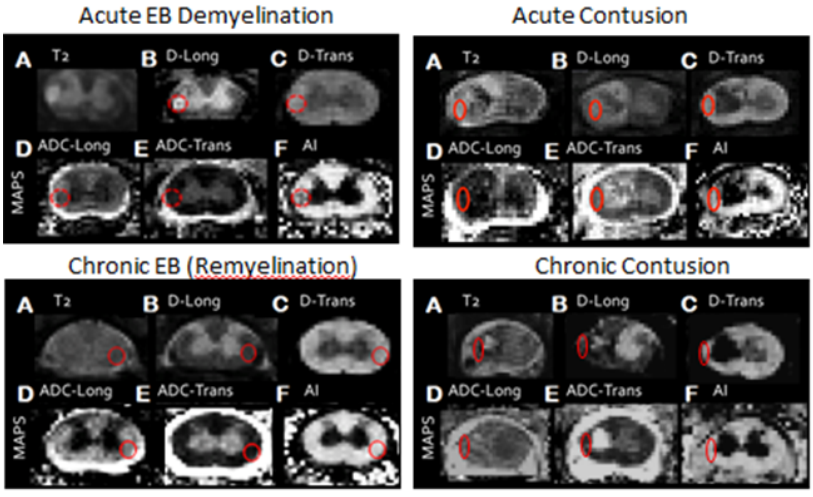

Figure 1: Sample T2 (*A*) and diffusion(*B,C*) sequences along with calculated ADC and AI maps (*D-F*) from the epicenter of acute EB (upper left), chronic EB (lower left), acute unilateral contusion (upper right), and chronic unilateral contusion (lower right) injury models. Red ovals approximate region of interest (ROI) analsysis for quantitative data.

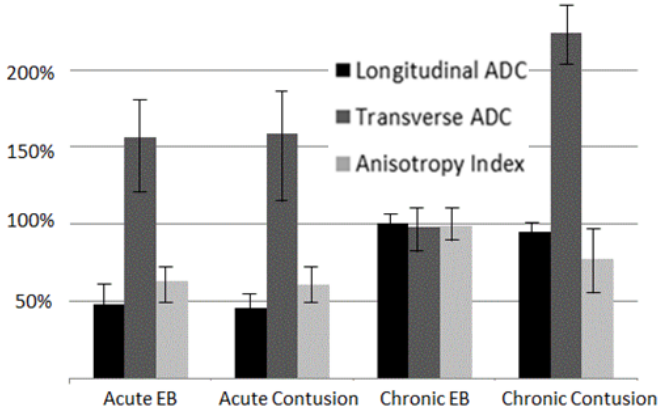

Figure 2: Longitudinal and transverse ADC values with associated anisotropy indices from lateral funiculus white matter after acute and chronic EB and contusion injury. Normalized values are graphed as a percentage of control. Error bars are normalized for ± 1 standard deviation.