Acute axial diffusivity changes predict long term locomotor function recovery after spinal cord injury

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Introduction After contusive spinal cord injury (SCI), the degree of axonal damage in ventral white matter (VWM) is crucial to the recovery of the hindlimb locomotor function in mice. Thus, a noninvasive assessment focusing on VWM axonal damage after contusive SCI during hyperaucte phase (0 – 6 hrs after injury) could potentially predict functional outcomes during this clinically relevant period. Diffusion tensor imaging (DTI) derived axial diffusivity describing water movement along the axonal fiber tract was proposed to be a potential biomarker of axonal injury (1). Recently, a modified behavioral assessment scale, the Basso Mouse Scale (BMS), has been demonstrated to be a sensitive, valid and reliable locomotor measure in SCI mice (2). Herein, the hyperacute VWM axial diffusivity and the chronic BMS assessment were evaluated.

Methods Fifteen eleven-week-old female C57BL/6 mice underwent dorsal laminectomy at the T10 vertebral level. Mice were equally divided into three experimental groups (n = 5 each) of sham, mild, and severe contusion SCI (1.3 mm diameter impactor tip at 0, 0.6, and 0.9 mm displacements) with a modified OSU impactor (2). Postoperative care procedures including manual bladder expression were performed daily. *In vivo* DTI data were acquired during the hyperacute phase (~2 hours after injury) and at chronic phase (14 days after injury). An inductively coupled surface coil (15 mm × 8 mm) was used as the receiver, covering the thorasic cord T7 through T11. A 9 cm i.d. Helmholtz coil was employed as the RF transmitter. A spin-echo diffusion-weighted sequence was used to acquire images with respiratory gating (3). All images were acquired with acquisition parameters of TR, 1.5 sec (gated acquisition), TE 38 msec, Δ 17 msec, δ 8 msec, slice thickness 0.75 mm, field-of-view 1 × 1 cm^2, data matrix 128 × 128 (zero filled to 256 × 256), total data acquisition time ~ 2.5 hrs. (Gx,Gy,Gz) = (1,1,0), (1,0,1), (0,1,1), (-1,1,0), (0,-1,1), and (1,0,-1), and b = 0 and .751 ms/μm^2. Image resolution was 78 × 78 × 750 μm^3. BMS was used to assess the locomotor function daily up to 14 days after laminectomy and contusion.

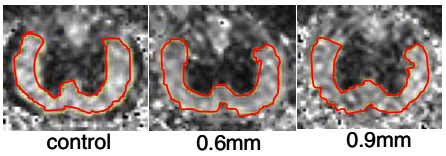

Figure 1 Hypercaute relative anisotropy (RA) maps show clear contrast between white matter and grey matter. RA decreases with increasing severity of the white matter injury.

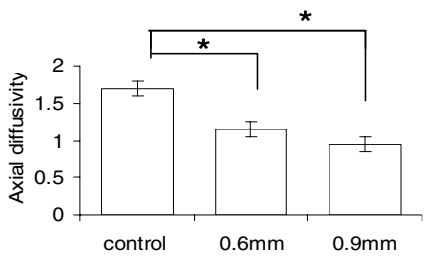

Figure 2 Hyperacute axial diffusivities in VWM of spinal cords from SCI mice. * p<0.02

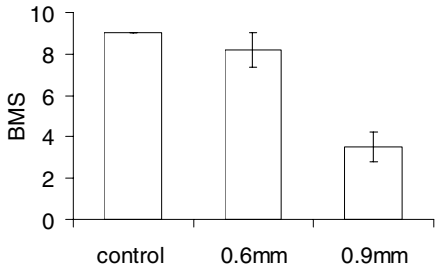

Figure 3 BMS (0 – 9) assessment of the three experimental groups of mice in chronic phase.

Results and discussion Relative anisotropy (RA) maps of sham and contusion injured mouse spinal cord (Fig. 1) demonstrate excellent contrast between gray and white matter in thoracic segment T10 at the hyperacute phase. RA decreased with increasing severity of the injury. The same ROI defined using the RA map was applied to the axial diffusivity maps for quantification. Axial diffusivity is significantly decreased in the VWM of the spinal cord from the injured animals. A trend of decreasing axial diffusivity with increasing severity is seen (Fig. 2).

The sham operated mice recovered from laminectomy without signs of disability as shown by the 14-day BMS scores (Fig. 3). For the mildly and severely injured groups, animals slowly regained their locomotion in the subacute phase (from 1 to 7 days after injury) and reached the stable BMS score at 7 or 8days after injury. Significant differences in locomotor outcomes between mild and severe SCI groups are evident as shown by the BMS scores. The mildly injured group shows close to normal BMS scores of 8 - 9. For the severely injured mice, BMS scores of 3 - 4 were recorded in the chronic phase (14 days after injury). A summary of the BMS scores of the three groups of animals are shown in Figure 3.

The current findings suggest that axial diffusivity reflects the severity of VWM injury of spinal cords from SCI mice in hyperacute phase. The extent of the decrease in VWM axial diffusivity, reflecting the severity of axonal injury, predicts the locomotor functional recovery, measured by BMS scores, of SCI mice. Axial diffusivity derived using DTI may be a useful biomarker of axonal injury and a possible surrogate end point for the outcome prediction.

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Reference

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2. Basso et al. *J Neurotrauma.* 23(5):635-59 (2006).