MR Detection of Spinal Axonal Degeneration in a Mouse Model of Amyotrophic Lateral Sclerosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease involving the selective loss of motor neurons in the cortex, brain stem, and spinal cord. Transgenic mice carrying the G93A-SOD1 mutation have been used as an animal model of ALS. As a neurodegenerative disease, biomarkers for ALS progression are lacking. Recent work suggests that *in vivo* MR-diffusion measurements can detect disease in the brain and cervical spinal cord (2, 3). However, it is likely that neurodegeneration may reach beyond the cervical spinal cord In the current study, we present directional diffusivities (λII and $\lambda\perp$) derived using *in vivo* diffusion tensor imaging (DTI) to evaluate the progressive degeneration of axons in thoracic spinal cord in G93A - SOD1 mice.

Methods

Five 4-month-old wild type mice and five age matched G93A-SOD1 transgenic mice underwent *in vivo* DTI evaluation at T12 and 13 vertebrae levels. DTI data were acquired using the set up as described previously (4). A spin-echo diffusion-weighted sequence was modified to acquire images with respiratory gating. All images were obtained with acquisition parameters of TR 1.2 sec (gated acquisition), TE 38 msec, Δ 18 msec, δ 7 msec, slice thickness 0.75 mm, field-of-view 1 $\times$ 1 cm^2, data matrix 128 $\times$ 128 (zero filled to 256 $\times$ 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 $\times$ 78 $\times$ 750 μm^3. After *in vivo* DTI measurements, mice were perfusion fixed and spinal cords harvested for histological validation of DTI findings.

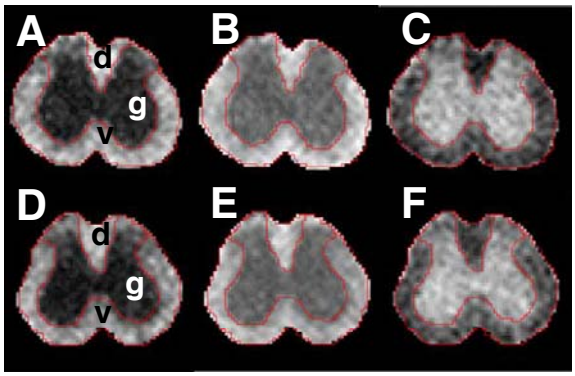

Fig. 1. The representative *in vivo* DTI maps of Wild (A - C) and G93A-SOD1 (D – F) mice. Relative anisotropy maps (A and D), axial (B and E), and radial (C and F) diffusivity maps are displayed. The d, v, and g represent dosal white matter, ventrolateral white matter and gray matter.

Table 1. DTI parameters at T12 and T13 vertebrae level.

		Wild	G93A-SOD1	*P*
	SNR	51 ± 3	55 ± 11	0.68
GM	**RA**	0.31 ± 0.1	0.29 ± 0.1	0.59
	λII	1.02 ± 0.1	1.01 ± 0.1	0.09
	λ⊥	0.61 ± 0.1	0.60 ± 0.1	0.48
DW	**RA**	0.98 ± 0.07	0.90 ± 0.02	0.04
	λII	1.82 ± 0.07	1.73 ± 0.99	0.17
	λ⊥	0.25 ± 0.05	0.29 ± 0.03	0.14
VW	**RA**	0.87 ± 0.03	0.79 ± 0.03	<0.001
	λII	1.78 ± 0.03	1.62 ± 0.05	<0.001
	λ⊥	0.33 ± 0.2	0.36 ± 0.2	0.02

Mean ± SD (n=5 for each group)
GM, DW, and VW represent gray matter, dorsal white matter, and ventrolateral white matter.

Results and Discussion

In vivo DTI maps provide excellent contrast between gray and white matter. Thus, the region of interest (ROI) could be readily delineated in both wildtype and transgenic mice (Fig. 1). Although not distinctively obvious, the difference between the WT and ALS mice can be seen qualitatively in the displayed DTI parameter maps (Fig. 1 it might help to put arrows here to point it out) in the ventrolateral white matter. The quantified DTI parameters at three different regions of the spinal cord are summarized in Table 1. The greatest decrease in axial diffusivity is seen in the ventrolateral white matter region with statistically significant deviation of λII, suggestive of significant axonal injury (4). Dorsal white matter values remained unchaged. These findings are consistent with the selective loss of motor axon fibers in the ventrolateral cord in ALS. Moreover, phosphorylated neurofilament (pNF) immunohistochemical staining revealed severe degeneration of axons selectively in the ventrolateral white matter in G93A -SOD1 transgenic mice (Fig. 2). Interestingly, there is no statistically significant difference in gray matter of T12 and T13 vertebrae levels where motor neurons of hind limb function are located. In conclusion, the current results suggest that *in vivo* DTI may be used to monitor the progression of neurodegenerative diseases such as ALS.

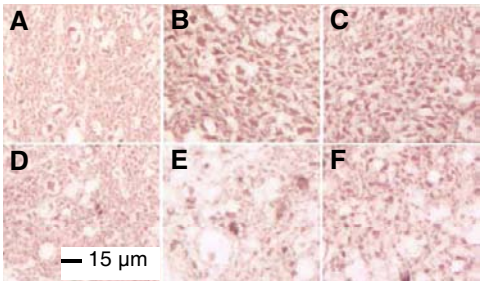

Fig. 2. The phosphorylated neuronfilament staining from wild type (A – C) and G93A-SOD1 (D – F) mice in dorsal (A and D) and Ventrolateral (B,C and E,F) white matter.

References

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3. Wang *et al.*, Ann. N.Y. Acad. SCI., 2005. 4. Kim *et al.,* Neurobiol. Dis., 2006.

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