MRI detection of neuronal degeneration in superoxide dismutase 1$^{G93A\ G1H}$ transgenic mouse model of amyotrophic lateral sclerosis

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Introduction: Amyotrophic lateral sclerosis (ALS) is a common form of motor neuron disease (MND). The superoxide dismutase 1 (SOD1) $^{G93A\ G1H}$ transgenic mouse is a widely used animal model of human ALS/MND [1,2]. Neuronal loss in both the spinal cord and brain stem have been found in this animal model by histology [2]. MRI T_2 hyperintensities in the brain stem of ALS patients have been reported [3]. The aim of this study is to investigate the use of MRI in detecting neuronal degeneration in the SOD1 mouse model.

Methods: Four 120 day-old SOD1 mice and three age-matched wild-type mice (control) were studied with a Bruker 4.7T BIOSPEC system using a microimaging probe. Axial T_2-weighted images were acquired using a RARE (fast spin echo) sequence with TR/TE=5000/54 msec, FOV=15x15 mm with 256x256 matrix (in-plane resolution of 58 μm) and slice thickness of 0.5 mm. The scanning time was 42 minutes with 16 NEX for 34 slices. Each mouse was anaesthetised and monitored (respiratory) during the scanning. Subsequently, the mice were sacrificed for histological examination with Nissl staining. The mouse brain was sectioned at 25 μm and immersed in 0.1% cresyl violet solution for 30 minutes before examination. The Howard Florey Institute Animal Ethics Committee approved this project.

Results: MRI T_2 hyperintensities were found in the brain stem in all four SOD1 mice (Fig. 1). These abnormalities correspond to the following nuclei: lateral paragigantocellular (LPGi), rostroventrolateral reticular (RVL), ambiguus (Amb), facial (7N) and motor trigeminal (Mo5) nucleus in the brain stem [4]. Histology analyses of the corresponding sites revealed marked neuronal degeneration. Other MRI abnormalities of atrophy were observed in the brain stem, cerebellum and cortex of the SOD1 mice (Fig.2).

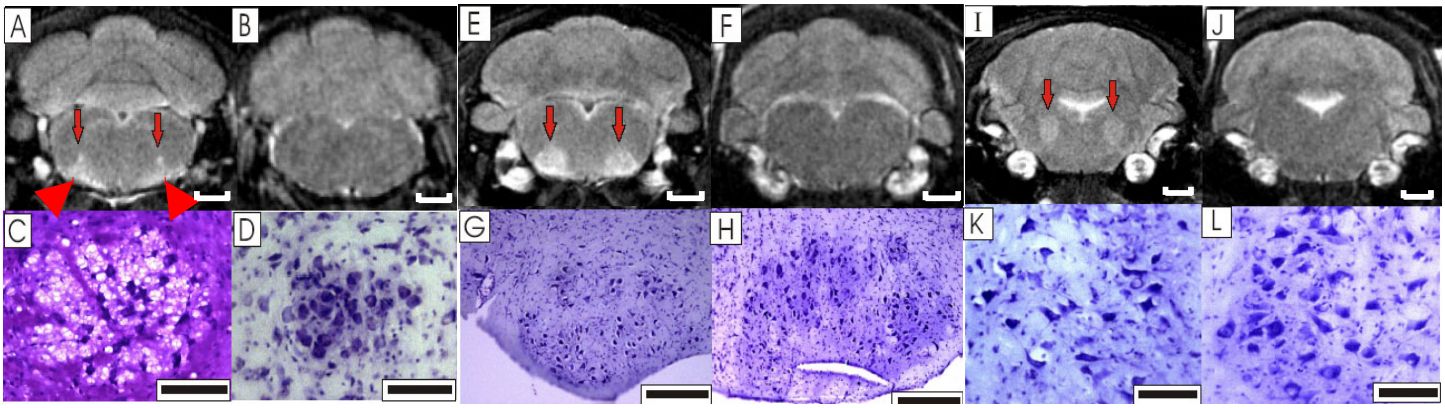

Fig. 1. Top row shows MRI T_2 hyperindensities in the Amb (A, arrow), LPGi and RVL (A, arrow head), 7 N (E, arrow) and Mo5 (I, arrow) nuclei of the SOD1 mice compared to control (B, F and J). Bottom row shows corresponding histology sections demonstrating neuronal degeneration in SOD1 mice (C, G, K) compared to control (D, H, J). All MRI scale bars are 1 mm. Histology scale bars are 50 μm (C, D), 100 μm (G, H), 20 μm (K, L).

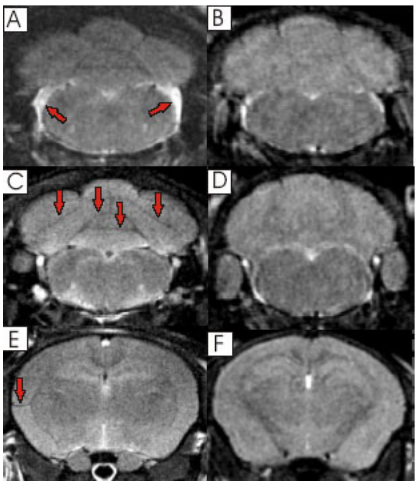

Fig.2 Atrophy in SOD1 mice with enlarged ventricle (A) and dark wrinkles in cerebellum (C) and cortex (E) compared with control (B, D, F).

Discussion:

MRI studies of the SOD1 mouse model of ALS have not been reported previously to our knowledge. In this report, we demonstrated MRI can be used to detect atrophy and neuronal degeneration in this model. Advanced imaging techniques including diffusion-weighted imaging and MR spectroscopy may further enhance the power of MRI as a non-invasive method for tracking disease pathology in the SOD1 mice model of ALS, enabling us to investigate disease progression and response to novel drug therapies.

References:

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