In vivo quantification of neuronal degeneration in the G93A-SOD1 transgenic mouse model of ALS by T_2 mapping

H. G. Niessen[1], F. Angenstein[1,2], K. Sander[2], H-J. Heinze[1], H. Scheich[2], S. Vielhaber[1]

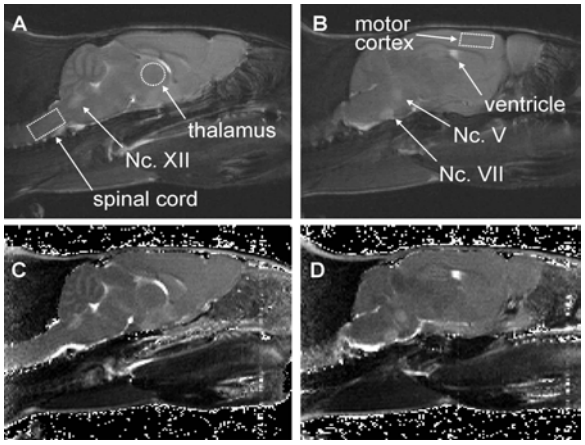
[1]Department of Neurology II, University of Magdeburg, Magdeburg, LSA, Germany, [2]Special Laboratory Non-Invasive Brain Imaging, Leibniz Institute for Neurobiology, Magdeburg, LSA, Germany

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a selective loss of motor neurons in spinal cord, brainstem, and motor cortex. The underlying mechanisms for the selective cell death of motor neurons are still uncertain [1]. For an independent evaluation of putative therapeutic approaches, sensitive and specific progression markers for the disease are a prerequisites. Recently, MRI became a powerful tool to study disease related alterations in brain structure and function [2]. In the most prevalent ALS model, the transgenic G93A-SOD1 mouse [3], neuronal degeneration of motor nuclei was recently visualized by T_2-weighted MRI [4,5]. However, the disease progression was only mirrored by a relative increase in signal intensity which did not allow for an absolute quantification of early neurodegenerative changes. In this study, we show that T_2 mapping yields suitable quantitative ALS progression markers in cortex, brainstem, and spinal cord.

Methods

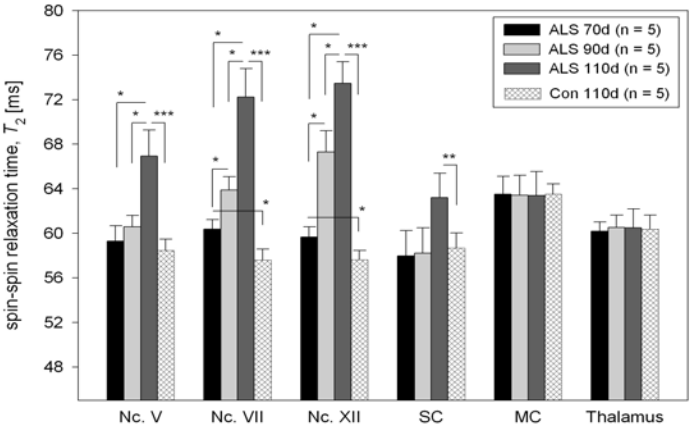
Transgenic B6SJL(G93A-SOD1) mice (n=5) and age-matched controls (n=5) were anesthetized with 1.5–2% isoflurane (in 70:20 N_2O:O_2). For anatomical orientation, sagittal T_2-weighted spin echo images were measured on a Bruker Biospec 47/20 scanner using a RARE sequence with the following parameters: *TR* 5000 ms, *TE* 20 ms, slice thickness 800 µm, interslice distance 200 µm, FOV 30x30 mm, matrix size 256x256, RARE factor 8, NEX 16. For three different time points after birth (70, 90, and 110 days) maps of T_2 were generated using 16 spin echoes and the following parameters: *TR* 4000 ms, initial *TE* 12 ms, *TE* increment 12 ms, matrix size 128x128, NEX 6. T_2 maps were calculated using a designated plug-in for the public domain software ImageJ. Afterwards, all maps were segmented to yield average values for a specific structure in the brain and upper spinal cord. For histology, frontal sections were cut at 40 µm and Nissl stained.



Results

Fig. 1 shows T_2-weighted MR images (A,B) and T_2 maps (C,D) obtained for a G93A-SOD1 mouse 110 days after birth. Fig. 2 shows the T_2 values obtained for three brain stem motor nuclei (Nc. V, VII, and XII), spinal cord (SC), motor cortex (MC), and thalamus 70, 90, and 110 days after birth (n=5) and for controls 110 days after birth (n=5); segmented brain regions are depicted in Fig. 1 A and B. Depending on the progression of the disease, ALS mice showed significantly increased values of T_2 in brain stem nuclei Nc. V (trigeminal nucleus), VII (facial nucleus), XII (hypoglossal nucleus), and the spinal cord; no change was observed in motor cortex and thalamus. Furthermore, in the upper spinal cord a dorsal-ventral difference with significantly higher T_2 values in the ventral part was demonstrated by T_2 mapping.

Fig. 1 (left): T_2-weighted MR-images (A,B) and corresponding T_2 maps (C,D) of transgenic G93A-SOD1 mice 110 days after birth.



Conclusions

Using T_2 mapping, neuronal degeneration in G93A-SOD1 transgenic mice is detected at least three weeks before day 90, i.e. clearly before the onset of clinical symptoms. For the evaluation of therapeutic approaches, it seems to be inevitable to use methods that can detect disease-related structural change as early as possible and to slow down the progression of ALS before clinical symptoms become evident. Consequently, by the determination of the T_2, progression markers are available for the screening of various putative treatments in the G93A-SOD1 transgenic mouse model of ALS.

Fig 2 (right): Histogram of T_2 times in various brain regions of G93A-SOD1 transgenic mice and controls

References

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