β-Amyloid Plaque Imging in a Transgenic Mouse Model of Alzheimer's Disease using MR Microscopy Without Contrast Reagent

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INTRODUCTION

The presence of amyloid plaques is one of the major pathogenic features of AD with neurofibrillary tangles and neuronal deficits. Due to the importance in visualizing these plaques for evaluation and assessment of possible therapeutic interventions of AD, much work has focused on developing an imaging technique to accomplish this. MRI can provide much higher spatial resolution than SPECT or PET without ionizing radiation, and several studies have demonstrated the feasibility of Aβ plaque imaging (1-3) using either relatively invasive methods for contrast reagent delivery or a prohibitively long scan time for *in vivo* applications. Therefore, we sought to image Aβ plaques without exogenous contrast reagents within a reasonably short scan time compatible with *in vivo* imaging.

METHODS

A total of seven 17-19 month old mice were studied: 4 doubly transgenic mice (PS/APP), 1 singly transgenic mouse (PS) and 2 non-transgenic (NTg) mice. At 17-19 months of age, the PS/APP mice exhibit numerous dense-cored plaques containing Aβ peptide within the cortex and hippocampus on the contrary to the PS mice that do not form any amyloid deposits. All experiments were performed at 7 Tesla (Magnex Scientific, Abingdon, UK & SMIS, Guilford, UK). T_2-weighted MR images were acquired using a multi-slice fast spin-echo (FSE) sequence. Image resolution was $54 \times 58 \times 200\ \mu m^3$ and $72 \times 78 \times 200\ \mu m^3$ with total scan times of 10 – 11 hrs and 2 – 3 hrs, for high and low resolution MR microscopy, respectively. To confirm the Aβ plaques in MRI, immunohistochemistry was performed on the same brain sections, which were immunostained by a standard avidin-biotin complex method.

RESULTS AND DISCUSSION

MR microscopy of Aβ plaques was achieved with careful adjustment of MR parameters of the FSE sequence for high SNR and contrast of the plaques. In the PS/APP mouse brain (Fig. 1A), numerous circular signal hypointensities were visible in cortical areas and hippocampus apart from white matter such as corpus callosum. In contrast to the PS/APP mouse brain, the PS mouse brain (Fig. 1B) and the NTg mouse brain (Fig. 1C) did not show any similar signal hypointensities in cortical areas or hippocampus. Similar patterns of signal hypointensities were identifiable in the non-fixed and non-perfused PS/APP mouse brains while no signal hypointensities were identifiable in PS or NTg mouse brains with the same preparation. This data supports the idea that there is negligible contribution from blood in vessels in the plaque image contrast (data not shown). For further validation that these signal hypointensities corresponded to the presence of plaques, MR images were compared with corresponding immunolabelled images. Co-registered high-resolution MR images and corresponding immunolabelled images from an 18-month old PS/APP mouse brain are shown in Fig. 2. Similar constellations of MR signal hypointensities and Aβ plaques can be seen from the magnified images of corresponding insets from MR and histology images.

In conclusion, we visualized Aβ plaques using a T_2-weighted imaging sequence in the fixed PS/APP mouse brain and demonstrated the presence of the Aβ plaque contrast in a non-fixed brain. The Aβ plaques in the MR images were confirmed by comparing the immunohistochemical analysis of the same brain sections. Toward true noninvasive in vivo imaging of plaques, the visualization of Aβ plaques was demonstrated in relatively short scan time of 2 – 3 hrs, in the fixed mouse brain.

REFERENCES

1. Benveniste et al, *PNAS* 1999; 96: 14079. 2. Poduslo et al, *Neurobiol Dis* 2002; 11: 315-329. 3. Wadghiri et al. *MRM* 2003; 50: 293-302.

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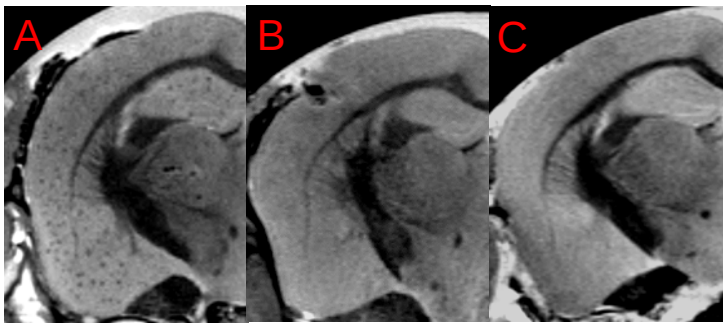

Fig. 1 MR microscopy images of fixed brains of a PS/APP mouse (A), a PS mouse (B), and a NTg mouse (C).

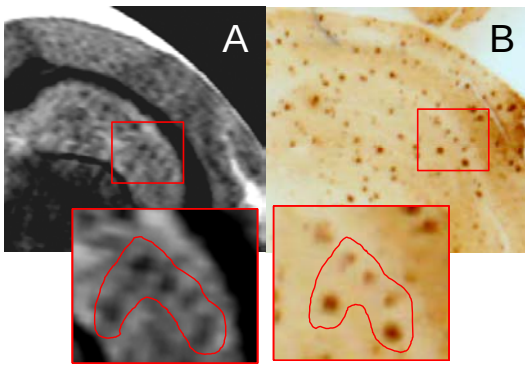

Fig. 2 Co-registration between MR microscopy (A) and histology (B) of a PS/APP mouse brain.