Longitudinal study of the development of beta-amyloid plaque burden in a transgenic mouse model of Alzheimer's disease, using *in vivo* magnetic resonance imaging

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and currently afflicts about 10% of the population over 60, with numbers still rising [1]. The neuropathologic features of AD include the occurrence of senile plaques, neurofibrillary tangles, decreased synaptic density, and loss of neurons. The core of senile plaques consists mainly of aggregated amyloidogenic peptide Aβ. Aβ plaque formation precedes disease onset by many years and is generally accepted as a biomarker for onset and progression of the disease [2, 3]. The development of non-invasive in vivo methods for imaging Aβ plaques has been a major challenge in recent years, with several groups developing magnetic resonance imaging methods for the visualization of Aβ [4, 5, 6, 7]. In this study we focus on developing magnetic resonance micro-imaging (μMRI) as a diagnostic tool for evaluating the progression of AD and the efficacy of putative treatment strategies. So far longitudinal studies were only possible by studying different animals from different age groups. μMRI presents the possibility of studying the development within the same animals, over time.

Methods

The transgenic mice used in this study (Tg2576) contain as transgene the Swedish double mutation of the human amyloid precursor protein (APP_{695}), as developed and described previously by Hsiao et al [8]. The transgene is expressed in C57B6 breeders. The N2 generation mice of both genders were studied at ages between 12 and 18 months. Age-matched non-transgenic littermates served as controls.

MR images were acquired using a 9.4-T vertical wide-bore imaging systems equipped with a Bruker Avance console and 1000-mT/m gradients. A series of coronal T_2-weighted images were acquired using the rapid acquisition with relaxation enhancement (RARE) sequence. The settings used were TE = 10.567 (22.45 ms effective), TR =6000 ms, RARE factor (echo train length) = 4 and averages = 4. An in-plane resolution was achieved of 78x78 μm with slice thickness of 200-500 μm in an acquisition time as low as 25 minutes. T_2 relaxation was measured using a Multi-Slice Multi-Echo sequence, with TE = 8.5, 17, 25.5, 34, 42.5, 51, 59.5, 68 ms, TR = 1500 ms, averages = 2, with an in-plane resolution of 78 x 78 μm and a slice thickness of 1 mm. Experiments were started at the age of approximately 12 months and repeated at 1 month intervals until the age of 18 months.

Following the MR experiments the animals were sacrificed and the brain fixed in buffered paraformaldehyde. Coronal sections (40 μm thick) were cut and stained using monoclonal anti-amyloid β (6E10) antibody to detect Aβ plaques.

Results and Discussion

Aβ plaques were detected with a scan time of as short as 25 minutes in the cortex and hippocampus of the living transgenic mouse. The distribution of plaques identified by MRM was in good agreement with that found in the immunohistochemically stained brain sections of the same animal (Fig. 1). Monitoring the plaques over age in the same animals showed that plaque burden increased markedly with age between 12 and 18 months in the hippocampus and cortex. Furthermore, an increase in the plaque load was associated with significant reduction in transverse relaxation time T_2 measured in the hippocampal and cortical regions (Fig. 2).

Conclusion

We have applied MR micro-imaging to follow the development of Aβ plaque burden in the brains of living transgenic AD mice without the aid of exogenous contrast agents in a reasonably short scan time. Our results show that the plaque developmental characteristics can be visualized in longitudinal studies using MR microscopy. Such MR longitudinal studies represent a valuable tool for evaluating the efficiency of novel anti-amyloid treatment strategies in arresting the growth or preventing the development of new plaques using AD mouse models. To our knowledge this work represents the first demonstration of utilizing MR to follow the development of Aβ plaque load over time, *in vivo* in the same animals.

References:

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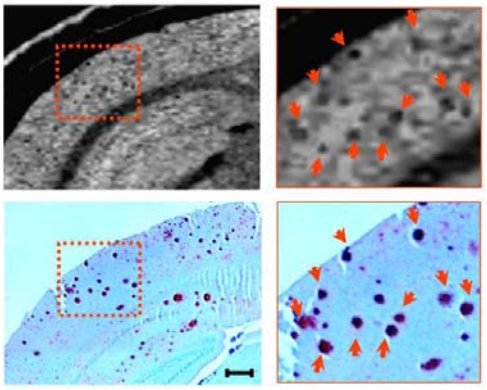

Fig. 1: Co-registration of μMRI with immunohisto-chemistry. Hypointensities seen on MR images correspond well with those seen in histology. Scale bar = 500 μm.

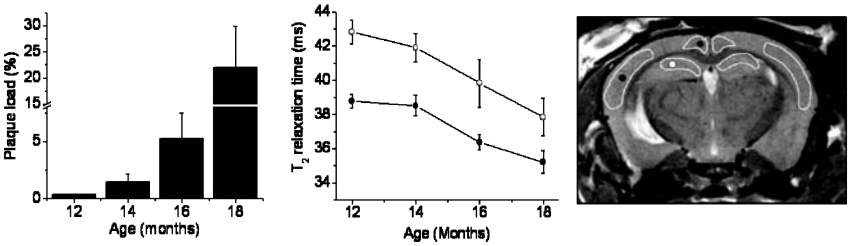

Fig. 2: T_2 values in the hippocampus (○) and cortex (●) regions of Tg2576 mice at ages 12, 14, 16 an 18 months. The decline in signal coincides with an increase in signal hypointensities in these regions (data not shown), corresponding to an increased plaque load.