In vivo MR Microscopy of Individual Alzheimer's Plaques in Transgenic Mice

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Introduction: One of the cardinal pathologic features of Alzheimer's disease (AD) is formation of senile, or amyloid, plaques. Murine models of AD have been created by inserting human mutations leading to familial AD into the mouse genome. Double transgenic mice [amyloid precursor protein (APP), presenilin 1 (PS1)] develop "human-like" plaque formation by 10-12 weeks of age, whereas plaques are not found in wild type mice[1].
Individual plaques can be resolved with MR microscopy in human AD autopsy brain specimens[2] and in ex vivo APP, PS1 mouse brain specimens[3-6]. We recently demonstrated that individual amyloid plaques can be resolved in vivo in APP, PS1 mice[7]. Intrinsic contrast between plaque and adjacent brain tissue is presumably due to iron content of plaques[2]. The purpose of this study was to characterize age dependent changes in the ability to visualize amyloid plaques in APP, PS1 transgenic mice with in vivo MR microscopy.
Methods: Wild type (WT) and APP, PS1 mice at ages 3, 6, 9, 12, 24, and 30 months were imaged in vivo and then ex vivo with previously described T2 –weighted spin echo and T2* -weighted gradient echo sequences specifically designed for this application[7]. Spatial resolution was 60x60x120 microns with scan time of approximately 1 hour. We evaluated the following features: 1) earliest age at which plaques could be resolved in vivo, 2) conspicuity of plaques in different brain regions (specifically, cortex, hippocampus, and striatum), 3) conspicuity of plaques on T2 vs. T2* sequences.
Results: Plaques appeared as small foci of decreased signal on both T2 and T2* images (Fig 1 and 2).
The appearance of plaques in the cortex and hippocampus was similar and differed from the appearance of plaque-like areas in the striatum. In the cortex and hippocampus, plaques were seen ex vivo at 6 months, but the earliest age at which plaques were visualized in vivo was 12 months. Plaque conspicuity increased with age after that point.
Plaques were not seen in wild type mice (Fig 3). Foci of decreased signal were visible in the striatum at 6 months on in vivo T2* images. These foci increased dramatically in size over time on both T2 and T2* images. These striatal deposits are specific to the APP, PS1 mice, as they were not present in wild type animals.

Fig 1. Ex vivo T2. APP-PS1 mouse, age 12 months. Cortical plaques are seen as dark foci. Arrows indicate individual plaques seen both ex vivo and in vivo (Fig 2).

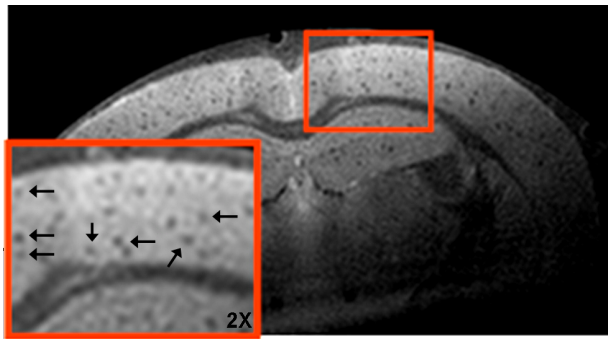
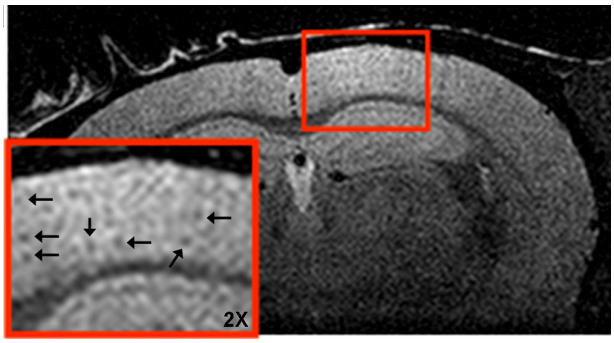
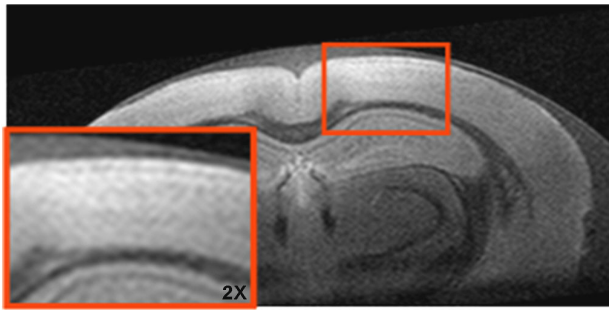


Fig 2. In vivo T2 (same mouse as in Fig 1). Spatially registered to ex vivo scan in Fig 1. Arrows indicate individual plaques seen both in vivo and ex vivo.



Discussion: The appearance of plaques on MR microscopy varies as a function of age and location in the brain. In theory, MR microscopy could be used to assess individual plaques over time in therapeutic intervention studies on transgenic mice. However, the natural history of plaque appearance on MR must be established first.

Fig 3. 12 month wild type mouse. Ex vivo T2. No plaques are seen.



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