Direct Visualization of Senile Plaques Using Clinical Field-Strength MRI and a Cholesterol-Fed Rabbit Model of Alzheimer's Disease

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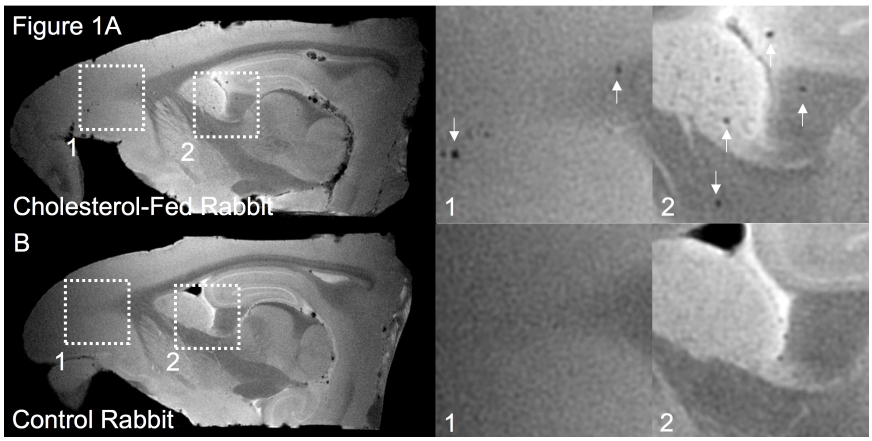
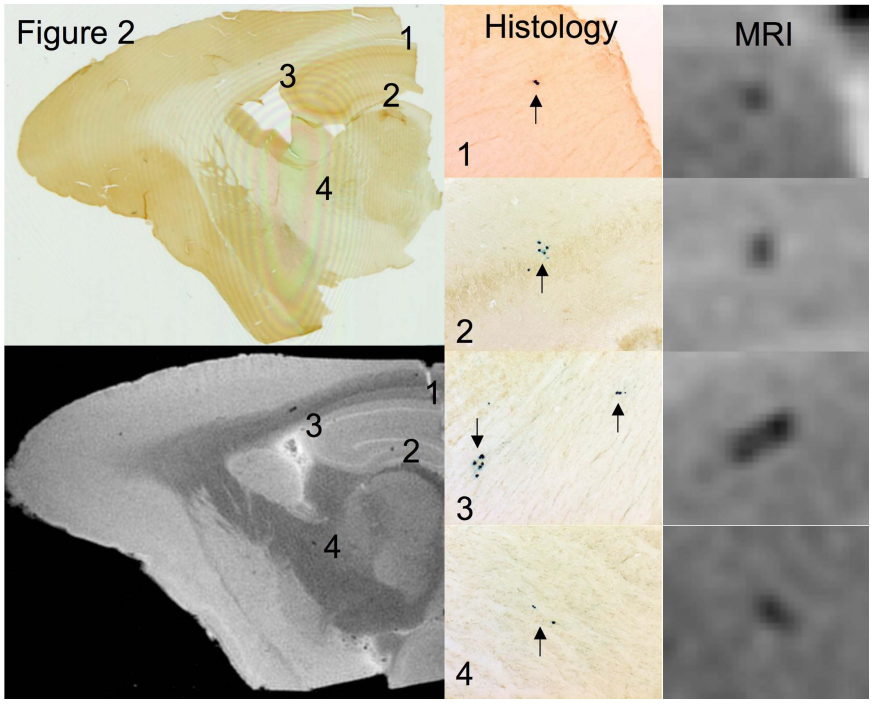
Purpose: A strong link exists between cholesterol (CH) metabolism and the pathogenesis of Alzheimers disease (AD). Patients with critical coronary artery disease have beta-amyloid (Aβ) deposition in their brains similar to that found in AD[1], statin therapy can abrogate these detrimental changes[2], and rabbits fed CH-enriched diets develop Aβ-enriched senile plaques in their brains[3]. While this latter model is considered more human-like than transgenic mouse models[4], it has the disadvantage that the high cholesterol diet (2% w/w) used to date leads to death of the animals (liver failure) shortly after the development of a significant number of plaques. Non-invasive direct detection of AD plaques has been demonstrated in murine brain using high-field MRI, probably due to the associated iron content in these plaques[5]. However, this observation has not been made in larger, spontaneous animal models or at clinical field strengths. Our goals in this study were two-fold: to establish a "survivable" model of AD using long-term low-level cholesterol feeding in rabbits; and to determine the feasibility of direct imaging of AD plaques using optimized iron-loaded cellular MR imaging protocols performed on a clinical field strength scanner.

Methods: Rabbits were fed either a low-dose CH-enriched (0.25% w/w) (n=5) or normal chow diet (n=4) for 27 months. *Ex vivo* MRI of half brains was performed on a 3T scanner interfaced with an insertable gradient coil (peak strength: 500 mT/m, peak slew rate: 3200 T/m/s) and solenoidal RF coil. 3DFIESTA (fast imaging employing steady state acquisition) images were acquired in 96 minutes (66x66x100 μm^3; TR/TE, 20/10 ms; FA, 20°; BW, 18 kHz; phase cycling number/recon, 10/sum-of-squares). Aβ-42 immunostaining and Prussian blue iron staining were performed consecutively on single brain sections.





Results: MR images (SNR~35) revealed distinct signal voids throughout the brains of the CH-fed animals, with voids primarily located in the hippocampus and adjacent cortex, striatum and thalamic regions (Figure 1A). Minimal voids were seen in the control animals (1B). The signal voids in MR images directly correlated to small clusters of Aβ-42-positive plaques, which were identified as iron-loaded compact plaques in matched brain sections (Figure 2). Individual plaques were typically around 10 microns in diameter.

Discussion and Conclusions: Rabbits fed a low-level CH diet over a long term develop Aβ-rich deposits that resemble compact plaques found in AD patients. These animals remain healthy, allowing the effects of treatment after disease establishment to be assessed in the future. Unlike mouse models, the rabbit model allows the link between CH metabolism and AD pathogenesis to be better explored. Minimal plaques were found in control animals suggesting that plaque formation may only be partially age related and that CH accelerates the development of these plaques. We show the first successful attempt at direct imaging of Aβ plaques formed in a large animal model of AD using high resolution MRI. Using technology primarily developed for imaging of iron-loaded cells, this is also the first successful imaging of plaques in any model at a clinical field strength, which was previously thought to be not feasible.

References:

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