Early detection of amyloid plaques in a transgenic mouse model of Alzheimer's disease

R. Chamberlain[1], S. D. Weigand[2], M. Marjanska[1], D. Reyes[3], T. M. Wengenack[4], G. Preboske[3], A. Snyder[1], G. L. Curran[4], C. O'Brien[4], J. F. Poduslo[4], M. Garwood[1], and C. R. Jack[3]

[1]Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, United States, [2]Division of Biostatistics, Mayo Clinic, Rochester, MN, United States, [3]Department of Radiology, Mayo Clinic, Rochester, MN, United States, [4]Departments of Neurology, Neuroscience, and Biochemistry/Molecular Biology, Mayo Clinic, Rochester, MN, United States

Introduction

Amyloid plaques are one of the hallmark pathologies of Alzheimer's disease (AD). Transgenic mice allow for controlled study of amyloid plaque formation. Magnetic resonance imaging is capable of imaging individual plaques in living transgenic mice non-invasively (1). Previous studies have shown that plaques can be resolved using a spin-echo sequence in living mice as young as 9 months, while histology indicates that plaques are present at 3 months of age (2). In this work we determined that plaques can be detected in vivo at 7 months of age using a new multi-asymmetric spin-echo (mASE) sequence (3).

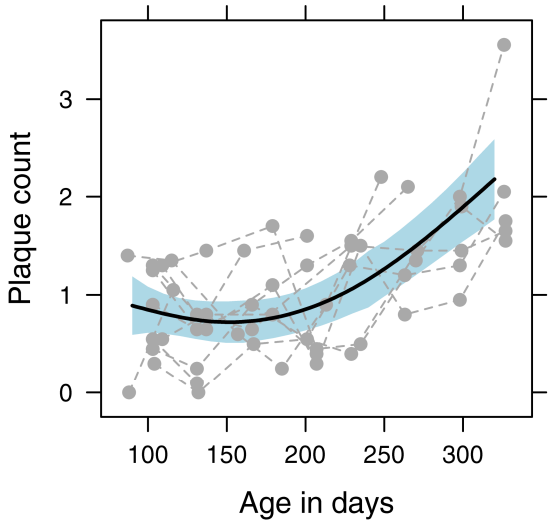
Methods

Eleven APP/PS1 mice were scanned at one month intervals from 3 months of age until 11 months of age at 9.4 T. Mice were immobilized and anesthetized for in vivo imaging. Imaging was performed with a mASE sequence with an echo train length equal to six. Each echo produced a fully-encoded image; after processing all the image sets were summed together to increase SNR. The echoes each had 4.5 ms of spin echo asymmetry to give a small amount of T_2^*-weighting. The pulse sequence was based on the previously described sequence (3) with an in-plane resolution of 60 x 60 µm, and a through-plane resolution of 100 µm. The imaging parameters were: TR = 1570 ms; sw = 30 kHz; x, y, and z matrices of 256 x 96 x 54 with an FOV of 15.36 mm in x, 5.76 mm in y, and 5.4 mm in z. Images were zero-filled to 512 x 192 x 54 before Fourier transform.

Plaques were counted by an observer blind to the age of the mouse by placing 20 ROIs in the cortex and manually counting the number of plaques within the ROI. The plaque count for the scan was defined as the average number of plaques per ROI. The data were fit with a linear mixed effects regression model to estimate the average plaque count per ROI as a function of mouse age measured in days. The age was treated as a fixed effect and modeled as a natural cubic spline with two knots in order to accommodate possible nonlinearity in the response over time. A likelihood ratio test was used to evaluate whether the spline fit was significantly better than a model that specified that plaque count was increasing linearly with time or constant with time.

Results and Discussion

The plaque counts are shown in the figure to the right. Each gray dot represents a plaque count for a scan, with the dotted lines connecting scans for the same mouse over time. The solid black line is the spline model that best fit the data with the solid blue region representing the 95% confidence interval for the spline fit. The spline model fit the data significantly better than a linear model ($P < 0.001$) or a constant model ($P < 0.001$). There are two distinct regions to this line: below 200 days the line is approximately flat. Conversely, above 200 days the mean plaque count increases at 0.0125 plaques per day per ROI. This indicates that below 200 days the imaging method is unable to reliably detect plaques. Around 200 days there are enough plaques present for the imaging method to reliably detect them.



The previously described single spin-echo technique (1) was able to detect plaques at 9 months of age, whereas the mASE technique was able to detect plaques two months earlier at 7 months of age. By virtue of greater sensitivity, the mASE sequence is a superior imaging tool for longitudinal studies where a younger starting age is beneficial. For example, studies investigating therapeutic prevention of plaque deposition should start at the earliest possible age plaques can be detected.

References

[1] Jack CR, *et al*, *MRM* **52**: 1263 (2004). [2] Jack CR, *et al*, *J Neuro* **25**: 10041 (2005).
[3] Chamberlain R, *et al*, ISMRM 2008.

Acknowledgements

Supported by NIH P41 RR008079 and P30 NS057091, the Keck Foundation, and the Minnesota Partnership for Biotechnology and Medical Genomics.