

Use of volumetric MRI to characterize treatment effect and phenotype in a transgenic mouse model of tau pathology

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INTRODUCTION:

Volumetric MRI (vMRI) is an important tool for in vivo characterization of brain morphology, and its relationship to normal physiology, pathology, and response to therapy. Of particular interest in the area of drug development for neurodegenerative diseases is the use of vMRI for characterization of longitudinal morphological changes in transgenic mouse models. In this work we studied rTg4510 mice, a regulatable transgenic mouse model of human tau pathology, a major hallmark of Alzheimer's disease. We explored longitudinal changes in vMRI, response to therapy (positive control and test compound) and relationship between vMRI measurements and post-mortem tau aggregation in the brain. Previous work on MRI analysis of transgenic mouse brain focused on comparison of different kinds of transgenic mice to wild type mice, and typically used high resolution (order of 10 μ m) images (Nieman et al, 2005). We evaluate the sensitivity of vMRI and associated automated analysis approaches in differentiating treatment groups as well as to characterize and phenotype the mouse model, while using a lower resolution (0.2 mm isotropic), high throughput imaging sequence.

METHODS:

All animal procedures were reviewed and approved by Merck's IACUC. A total of 44 rTg4510 mice were randomly assigned to four groups with 11 animals each, vehicle (negative control), Doxycycline (positive control), and two doses (low and high) of a test compound (Rx). Whole head images of the mice were acquired using a quadrature mouse head surface-receive coil (Rapid Biomedical). A RARE sequence with an inversion preparation pulse for enhancement of CSF contrast was optimized to render high tissue contrast, high throughput, and reasonable spatial resolution (TR/TE/TI=2500/50/334 ms; RARE factor=16; 3D acquisition; 75x100x60 matrix; 15x20x12 mm³ FOV). Final isotropic resolution was 0.2 mm at scan time of 10 min. Scans were performed at 9, 18, and 24 weeks of age. Biochemical endpoints of soluble (55KD) and insoluble tau (64KD) concentration levels were detected by Western Blot at week 24. Fully automated, atlas based segmentation with diffeomorphic demons non-rigid registration algorithm was used to segment the brain into 7 regions of interest (ROIs) including forebrain (FB), cortex (CTX), ventricle (VNT), hippocampus (HC), and cerebellum (CBL). Repeated measures ANOVA was used to assess longitudinal and differential treatment effects. ROI volume data from all treatment groups were pooled together and regression analysis was used to probe correlation between ROI volume and tau burden.

RESULTS and CONCLUSIONS:

In Figure 1, results for treatment group effect for bulk FB (1a) and ROI volume correlation with soluble tau (55KD) for FB (1b) and CBL (1c) are shown, along with transaxial sections of example MR images from Vehicle and DOX groups, overlaid with an outline of the DOX subject brain on both images (1d). Average percent changes in ROI volumes cross sectionally (at week 24) and longitudinally (between week 18 and 24) are summarized in Table 1(e), along with the correlation of each ROI volume at week 24 with soluble tau levels. Significant differences ($p < 0.001$) are indicated in bold. In the vehicle treated group, we found that the rTg4510 mouse model exhibits atrophy in FB and CTX, and increase in VNT volume (not shown) from week 18 to week 24, with $p < 0.0005$. The positive control (DOX) showed differentiation from the vehicle treatment group in the FB, HC, and CTX regions, with DOX having significantly higher volume ($p < 0.0001$) than vehicle in these regions at week 24. Treatment with either dose of the test compound yielded longitudinal profile of ROI volumes no different from vehicle. Additionally, CTX, FB, HC volume showed significant negative correlation with soluble tau (55KD) levels while CBL did not. The data acquisition and processing pipeline described above yielded quantitative endpoints (biomarkers) that were sensitive to positive control therapy (DOX). The test compound in this study (Rx) proved non-efficacious at both doses. Our results also highlight specific brain ROIs (FB, CTX, HC) that respond to therapy and show high correlation with biochemical phenotype (tau burden). These biomarkers and ROIs should be the focus of future studies of novel therapies in this animal model.

