Longitudinal Changes in Glutamate in a Mouse Model of Tauopathy Measured by GluCEST
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BACKGROUND: Tauopathy is a broad category of dementia disorders characterized by the presence of intracellular aggregates of tau protein, which includes Alzheimer’s disease (AD), Corticobasal degeneration, and Down’s syndrome. The PS19 mouse model is a transgenic mouse which overexpresses mutated human tau, at P301S, a common mutation in FTDP-17 patients [1]. When expressed in a congenic background, PS19 mice develop pathology between 6-9 months of age, and with progressive synapse and neuron loss up to 15 months. Here we have studied this quickly progressing mouse model longitudinally, using GluCEST and 1H MRS to measure the effects of progressive tau pathology on glutamate levels.

METHODS: All animal studies were approved by the university’s IACUC. Glutamate was measured in congenic PS19 mice and age-matched wild-type mice at 3 and 7 months old (Cohort 1: n=6 WT, n=6 PS19), and another cohort at 10 and 13 months old (Cohort 2: n=3 WT, n=6 PS19). In vivo measurement of glutamate levels from 3mm of the hippocampus was carried out using proton magnetic resonance spectroscopy (1H MRS) and glutamate chemical exchange saturation transfer (GluCEST) MRI. Imaging was performed on a 9.4T spectrometer (Varian Inc., Palo Alto, CA). MRS was performed using the PRESS pulse sequence (TR/TE 3000/14ms, 256 averages), with VAPOR water suppression, while gating with respiration. GluCEST imaging was performed using a custom-programmed RF spoiled gradient echo readout pulse sequence, with a frequency selective continuous wave saturation preparation pulse. CEST images were collected using a 1 second saturation pulse at peak B1 of 250 Hz for the frequencies ± 2.5 – 3.5 with steps of 0.25ppm from water resonance. B1 and B0 maps were acquired to correct inhomogeneities. All images and spectroscopic data were processed as described previously [2]. Cohort 1 will complete two additional time-points of imaging, and immunohistochemistry will be used to analyze pathologic correlates from all brains.

RESULTS:

CONCLUSIONS: Glutamate increases during neuronal development of adolescent mice, and decreases in the thalamus/hypothalamus with the progression of tau pathology. In two cases, extremely low GluCEST values predicted early disease onset. Continuing study of cohort 1 will confirm whether glutamate changes after pathology increases in severity. Immunohistochemistry will be performed to correlate glutamate loss with tau pathology, synapse, and neuron loss throughout the brain.

REFERENCES: