Developing Protein-based MRI Biomarkers for Alzheimer's Disease

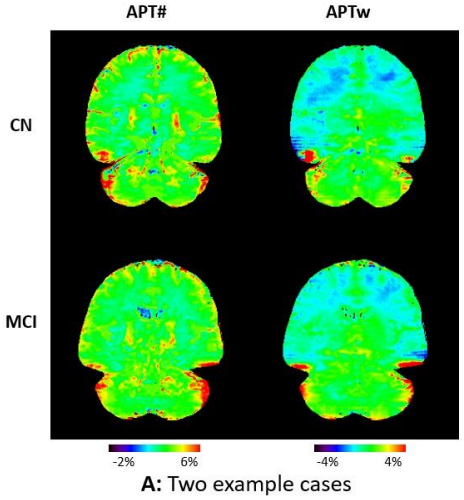
Jingpu Wu,[1] Puyang Wang,[1] Shanshan Jiang,[1] Jinyuan Zhou[1]
[1] Johns Hopkins University, Baltimore, MD, USA

INTRODUCTION:

The hallmarks of Alzheimer's disease (AD) are the gradual accumulation and aggregation of toxic soluble and insoluble beta-amyloid (Aβ) and tau species in the brain. Amide proton transfer (APT) imaging is a relatively new protein-based molecular MRI technique that is based on endogenous mobile proteins and peptides in tissue. It is known that both extracellular Aβ and intracellular tau first exist as soluble monomers and oligomers,[1,2] which are APT-detectable. This study was performed to examine whether APT signal can be a surrogate biomarker for early AD diagnosis.

METHODS:

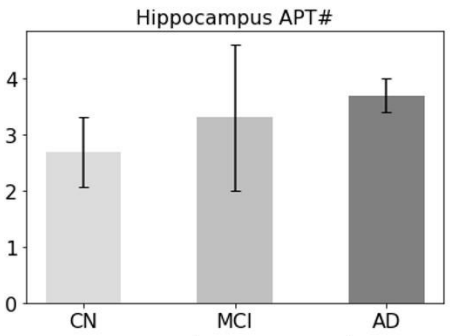
MRI experiments were carried on a Phillips 3T MRI scanner. Coronal 3D APT images (RF saturation power = 1.5 μT; saturation time = 1.5 sec; 24 offsets; 15 slices) were acquired. WASSR images were acquired for correcting B0 inhomogeneity. The conventional APT-weighted image is defined as: APTw = $MTR_{asym}(3.5ppm) = [S_{sat}(-3.5ppm) - S_{sat}(+3.5ppm)] / S_0 = Z_{exp}(-3.5ppm) - Z_{exp}(+3.5ppm)$. Based on the extrapolated semi-solid magnetization transfer reference (EMR) approach, the Z-spectrum data of seven large, positive offsets (80~8 ppm) were fitted with a super-Lorentzian line shape, leading to a reference curve (Z_{EMR}). Then, $APT^{\#}$ and $NOE^{\#}$ were calculated: $APT^{\#} = Z_{EMR}(3.5ppm) - Z_{exp}(3.5ppm)$ and $NOE^{\#} = Z_{EMR}(-3.5ppm) - Z_{exp}(-3.5ppm)$. T1 and T2 maps were also acquired. ROIs (hippocampus) were manually drawn on both sides. The mean values of T1, T2, APTw, $APT^{\#}$, $NOE^{\#}$ and MTR at 20ppm in the ROIs were counted. Group-based analysis of these values were performed.



A: Two example cases

RESULTS:

31 participants were included, 23 cognitively normal controls (CN), 5 mild cognitive impairment (MCI) and 3 AD. MCI had higher $APT^{\#}$ signal intensity values than CN in multiple brain regions while AD had even higher values (in hippocampus, p = 0.11 and < 0.01, respectively, based on the limited sample size). APTw values were smaller than $APT^{\#}$, but there was a similar trend. This may be attributed to the abnormal accumulation of various mobile proteins, including soluble Aβ and tau oligomers, with the progress of AD. Besides, $APT^{\#}$ signal values showed a correlation coefficient of -0.524 with the mini mental state examination (MMSE) score and 0.496 with the Clinical dementia rating (CDR). Patients with more severe cognitive impairment tended to have higher $APT^{\#}$ values. Inclusion of more MCI and AD cases and correlation analysis with amyloid and tau biomarkers in CSF are needed to further validate the results.



B: Comparison of mean APT# values. CN vs. MCI (p=0.11), MCI vs. AD (p=0.67), **CN vs. AD (p=0.01)**

Based on the definition, APTw = $APT^{\#}$ - $NOE^{\#}$. This suggests that the EMR-APT approach can achieve purer and higher APT signals than simply using the conventional APTw metric.[3,4] In addition, our recent study demonstrated that the deep-learning-based EMR method achieved high reproducibility and reliability in the quantification.[5]

DISCUSSION AND CONCLUSION:

The early results showed that APT imaging may detect an increased signal that may reflect soluble Aβ and tau proteins in MCI and AD and have the potential to track decreases in these abnormal protein levels during anti-amyloid immunotherapy against AD.

ACKNOWLEDGMENTS:

Thank Isabel M. Rios Pulgar, Carrie Wagandt, Greg Pontone, Arnold Bakker, Munendra Singh, Hye-Young Heo, Kenichi Oishi, Arvind Pathak, Gwenn Smith, Chiadi Onyike, Jee Bang, and Abhay Moghekar for cooperation on this project. This study was supported partially by grants from the NIH (R01AG06917 and UH3NS106937).

REFERENCES:

1. Hampel H et al. Mol Psychiatry. 2021;26:5481-503; 2. Gandy S et al. N Engl J Med. 2023;388:80-1; 3. Wang R et al. Chin Med J. 2015;128:615–9; 4. Zhang Z et al. NeuroImage: Clinical. 2020; 25:102-153; 5. Heo et al. Magn Reson Med. 2024;91:1002-15.