Assessment of early cerebrovascular alterations and β-amyloid accumulation in Alzheimer’s disease

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Cerebrovascular alterations, one of the risk factors for Alzheimer’s disease (AD) pathogenesis, is classified as early change in AD progression. Aging, the main risk factor for AD, slows the velocity of cerebral blood flow, which may be more deteriorated by cerebrovascular impairments and related with AD pathology cascade. The sluggish blood delivery to the tissue can facilitate β-amyloid (Aβ) accumulation and inhibit Aβ clearance. Since the brain attempts to maintain cerebral blood flow (CBF) homeostasis by regulating the caliber of cerebral arteries and arterioles, in early stage of cerebrovascular alterations, cerebral arterial blood volume (CBVa) could be increased to compensate for slow blood. Detailed characterizations of early cerebrovascular alterations, which has been limited to only CBF measurement, could potentially provide a better understanding of AD pathophysiology.

Mild cognitive impairment (MCI) subjects and healthy controls were studied on a 3T system using a 32-channel head coil. The pulsed Look Locker (LL)-ASL technique measures the evolution of ASL signal by acquiring data at multiple inversion times (TIs) after a single spin labeling pulse. Data (GE-EPI) was acquired with 15 readout steps after spin labeling with the time interval between TIs = 259 ms using multiband acquisition technique (acceleration factor = 5) with and without bipolar gradients alternating to separate the arterial component (b = 3 s/mm²). ASL models are fit to ROI averaged ASL signals using a least-squares fitting algorithm. Modified Gaussian dispersion model was used to incorporate the dispersion effects for arterial blood and tissue. [C-11] (Pittsburgh compound-B) PiB-PET data was acquired on a mCT PET/CT scanner and regional standardized uptake value ratio (SUVR) outcomes normalized by the cerebellum reference SUV were generated.

MB LL-ASL technique can visualize differences in the perfusion dynamics between MCI and controls. Fig. 1 shows visual differences in the ASL dynamics maps for arterial blood (above) and tissue (below) signal between MCIs and controls with 259ms of temporal resolution for whole brain. The evolution of arterial blood delivery and the progression of tissue perfusion for whole GM and two ROIs, precuneus and anterior cingulate, are shown (Fig. 1C). Overall, the MCI subjects had slower delivery of arterial blood, lower CBVa and prolonged capillary transit times in comparison to control subjects. The relationship between PiB SUVR and metrics for ASL dynamics were measured for multiple ROIs. Various distributions of the metrics of ASL dynamics were observed despite normal PiB retention, while MCI with high PiB retention showed altered cerebrovascular responses for all metrics. This suggests that alterations in ASL dynamics may be earlier disease progression before PiB retention.

Detailed regional assessments of cerebrovascular alterations across whole brain provide better characterization of early cerebrovascular physiology in AD. The relationship between these vessel changes and amyloid accumulation provides a better understanding of the pathogenesis and progression mechanism of Alzheimer's disease.
Fig. 1. The measured arterial blood signal dynamics at 15 different TIs (13 TIs are displayed) from one control (A) and MCI (B). 3 out of 20 slices are displayed. (C) Averaged arterial blood (red circles) and tissue (blue circles) signals show the process of arterial blood and its delivery to tissue and the fitted curves from control (solid line) and MCI subjects (dotted lines). The delayed arterial delivery induces lagged tissue perfusion. Overall, sluggish ASL signal dynamics and lower CBVα were observed in the MCI subject.

Fig. 2. PiB-PET and corresponding T1-weighted images. (A) healthy control, 70 old, Female, MMSE = 29. (B) MCI, 72 old, Male, MMSE = 26. color scale: SUVR

**Keywords**: Arterial spin labeling Cerebrovascular alterations Alzheimer’s disease PiB-PET
Translational and Applied MR Research in Neuro-oncologic Imaging

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Translational research is about translating progress in basic research into products and procedures that benefit patients. However, limited understanding of the oncogenesis of cancer is a key roadblock to effective translational research. When the basic research enterprise identifies a key step of oncogenesis and a druggable molecular target, the pharmaceutical and biotechnology industries are usually adept at developing potent inhibitors of that target. In neuro-oncologic imaging field, recently, one of the issues is investigating the glioma neo-angiogenesis by contributing of tumor-associated macrophages (TAM) for implicating for anti-angiogenic strategies. Gliomas are characterized by extensive neo-angiogenesis, and knowledge of the role of TAMs in neovascularization is important for future anti-angiogenic therapies. However, many studies have reported that the phenotypes and functions of TAMs are heterogeneous and more complex than a classification into M1 and M2 inflammation response types. In this lecture, I provide a basic research which is assessment of the effects of chemokine ligand 2 (CCL2) inhibition as a combination therapy with bevacizumab for the treatment of glioblastoma (GBM), which was correlated with DSC perfusion MRI. For this research, we used a CCL2 inhibitor, mNOX-E36, to suppress the recruitment of CCL2-dependent macrophages and investigated the short-term effect of combination therapy of the CCL2 inhibitor with bevacizumab by using DSC perfusion MRI in CCL2-expressing rat GBM model. In addition, we also correlated the CCL2 expression and recruitment of macrophages with DSC perfusion MRI in GBM patients for investigating potential therapeutic targets to TAM-regulated tumor angiogenesis in clinical field.

Keywords: Translational Research, Neuro-oncologic imaging, Perfusion MRI, Radiogenomics
Application of Size-controlled Melanin Nanoparticles as T1 MRI Contrast Agent

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Development of new class of biocompatible and functional T1 MRI contrast agent has been a crucial issue in diagnostic imaging, since Gd³⁺ based agents were subjected to not only health but also environmental issues. Even though magnetic nanoparticles composed of inorganic metal oxide (e.g. Fe₃O₄, MnO, and etc) suggested impressive applications in molecular imaging in past decades, their practical efficacies have been controversial because of their negative contrasting ability and latent toxicity issues. However, our melanin-like nanoparticles (MelNPs) generated by spontaneous oxidation of dopamine, resemble natural sepia, are biocompatible organic nanomaterial, and subsequently, have a promising future for clinical uses. In this work, we introduce our newly developed MRI T1 contrast agent and its in vivo MRI of liver and brain in mouse tumor models.

By exposure to alkaline condition, MelNPs can be disintegrated into protomolecules with thickness less than 3 nm. After PEGylation followed by complexation with Fe³⁺ ion, they were injected into liver and brain tumor models respectively.

Size-controlled MelNPs enhanced the normal liver initially, and the delayed signal enhancement in tumor tissue at 24 h post injection. In contrast to liver tumor model, size-controlled MelNPs caused the instantaneous signal enhancement around brain tumor up to 2 h after intravenous administration, which is similar with the results by Gd-based contrast agent. Transient signal enhancement around brain tumor would be attributed to defective blood-brain barrier (BBB), which enables extravasation of small MelNPs leading to accumulation in the extravascular extracellular space.

Our findings indicate that size-controlled MelNPs may serve as a new type of T1 MRI contrast agent. High biocompatibility and unique ability to visualize the tumors with high selectivity would make melanin-based contrast agent promising T1 contrast agent for clinical use.

Keywords: MRI, T1 MRI contrast agent, Melanin, Melanin-based T1 contrast agent