Chemical Exchange Saturation Transfer MR Imaging of Alzheimer¡¯s Disease at 3 Tesla: a Preliminary study

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Background and purpose

Alzheimer's disease (AD) is known as the leading cause of dementia in elderly. Although there are no effective treatments for AD yet, earlier treatment can hamper the disease process and improve disease prognosis, and hence, the early diagnosis of AD is of a high clinical importance. Amide proton transfer (APT) imaging is a novel molecular MRI technique that detects low-concentration endogenous mobile proteins and peptides in tissue to indirectly reflect intracellular metabolic change and physiological and pathological information in vivo.[1] Most current studies about APT focus on tumors and stroke.[2] No study has been published about using APT imaging on AD patients yet. This study aimed to test the feasibility of using APT imaging to detect cerebral abnormality patients in Alzheimer's disease (AD) at field strength of 3 Tesla.

Methods

Twenty AD patients and 20 healthy elderly subjects were enrolled in the study. The demographics and neuropsychological findings of AD patients and healthy elderly subjects are shown in Table1. The MR examinations were performed on a 3.0-T MRI system (Achieva TX, Philips Healthcare, Best, The Netherlands), using an eight-channel head coil. APT imaging was based on a single-shot, turbo-spin-echo readout, with the following parameters: repetition time 3000 ms, turbo-spin-echo factor 54, field of view 230mm × 220 mm, matrix 105 × 100; slice thickness 5mm. We used a pseudo-continuous wave, off-resonance RF irradiation (saturation duration 200 ms × 4, inter-pulse delay 10 ms, power level 2 μT) and a multi-offset, multi-acquisition APT imaging protocol. The axial scanning plane is parallel to the long axis of the hippocampus(Hc). The T1-weighted image was used as the anatomical reference to draw regions of interest of bilateral Hc, temporal white matter (TWM), occipital white matter (OWM） and cerebral peduncles (CP) on the oblique axial APT image, as shown in Figure1. MTR_{asym}(3.5ppm) were measured for each region. The average MTRasym(3.5ppm) and corresponding 95% confidence intervals were calculated for each region. MTR_{asym}(3.5ppm)of cerebral structures in AD patients and control subjects were compared using the independent samples *t* test. Controlling for age, partial correlation analysis was used to investigate the associations between MMSE and the various MR imaging measures among patients with AD. The level of significance was set at $P < 0.05$.

Results

We found that the MTR_{asym}(3.5ppm) values of bilateral Hc were significantly higher in AD patients than in normal controls. The additions are equivalent to approximately 49% for the right Hc and 47% for the left Hc respectively. However, no significant differences in MTR_{asym}(3.5ppm) values of other brain structures were observed between AD patients and normal controls(Table 2). MTR_{asym}(3.5ppm) of bilateral Hc were significantly associated with MMSE (right r=-0.559, *P*=0.013; left r=-0.461, *P*=0.047). There were no correlations between MMSE and MTR_{asym}(3.5ppm) values in bilateral TWM, OWM and CP.

Discussion and Conclusions

Our results showed that compared to normal controls, MTRasym(3.5ppm) values of bilateral hippocampi were increased in AD patients. In contrast, There was no significant statistically difference in MTRasym(3.5ppm) values of other cerebral structures between AD patients and control subjects. There may be two reasons for the findings: 1. The hippocampus is affected the earliest and most severely in AD patients.[3] 2. Elevated MTRasym(3.5ppm) values of the hippocampi in AD patients may be associated with increased cytosolic proteins and peptides, including Aβ oligomer, Tau, a-synuclein, TDP-43, and so on.[4-6] In conclusion, the APT imaging, as a non-invasive MRI method, can provide unique image contrasts that reflect the changes in cytoplasmic proteins and peptides in specific brain regions of AD patients, suggesting that APT may serve as a tool to diagnose AD and monitor the disease progression.

Table1. Demographics and neuropsychological findings of normal subjects and AD patients

Groups	normal subjects	AD patients	*t*	*P*
Age (years)	71.9±5.0	73.7±4.7	1.175	0.247
Male/Female (n/n)	11/9	9/11	0.400*	0.527
MMSE	16.9±7.0	28.6±1.0	-7.283	0.000

Note: * Two-sample t test for all comparisons except sex, where Pearson $\chi 2$ test was used.

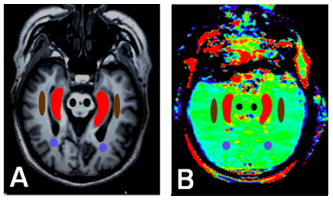

Figure1. T1WI(A) and APT image(B) were oblique axial planes along the long axis the Hc. Examples of the definition of regions of interest for quantitative analysis. Brown: TWM, purple: OWM, black: CP, red: Hc.

Table2. MTR_{asym}(3.5ppm) (%) of bilateral Hc, TWM, OWM and CP in normal controls and AD patients

	Control Subjects	Patients with AD	*t*	*P*
Right Hc	0.83±.0.19	1.24±0.21	3.039	0.004*
Left Hc	0.80 ± 0.17	1.18±0.18	3.238	0.002*
Right TWM	0.39 ± 0.08	0.42±0.09	0.636	0.529
Left TWM	0.34±0.06	0.38±0.10	0.699	0.489
Right OWM	0.32±0.07	0.36±0.12	0.591	0.558
Left OWM	0.38± 0.09	0.34±0.09	0.604	0.549
Right CP	1.03±0.15	1.14±0.22	0.778	0.442
Left CP	1.09±0.19	1.19±0.21	0.703	0.487

References

1. Zhou J, Payen J, Wilson DA, et al. Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. Nature Med, 2003; 9(8):1085-1090.
2. Zhou J, Tryggestad E, Wen Z, et al. Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides. Nature Med, 2011; 17(1): 130-134.
3. Du AT, Schuff N, Amend D, et al. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry, 2001; 71(4): 441-447.
4. Larson ME, Lesné SE. Soluble Aβ oligomer production and toxicity. J Neurochem, 2012; 120(Suppl 1): 125-139.
5. Köpke E, Tung YC, Shaikh S, et al. Microtubule-associated protein tau: Abnormal phosphorylation of non-paired helical filament pool n Alzheimer disease. J Biol Chem, 1993; 268(32): 24374-24384.
6. Xu G, Stevens SM Jr, Moore BD, et al. Cytosolic proteins lose solubility as amyloid deposits in a transgenic mouse model of Alzheimer-typeamyloidosis. Hum Mol Genet, 2013; 22(14): 2765-2774.