CSF biomarkers associate with GM volume and brain microstructural changes mainly from Default Mode Network in Alzheimer's disease

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Introduction:

Alzheimer's disease (AD) is the most common dementia in elderly people. The pathological hallmark of AD is amyloid plaques and neurofibrillary tangles, which are made up of -amyloid$_{1-42}$ (A42) and tau phosphorylated at position threonine 181 (p-tau), respectively [1]. Such brain changes occur decades before the onset of dementia and could be reflected by the cerebrospinal fluid (CSF) biochemical changes. Decreased levels of A42 and increased levels of total tau protein (T-tau) and p-tau in CSF are useful and valid tool for the diagnosis and prognosis of AD. Mild cognitive impairment (MCI) is recognized as the prodromal stage of AD. There is evidence indicating that subjective cognitive impairment (SCI) is a stage prior to MCI in the eventual development of AD dementia. A CSF AD profile is also common in patients with MCI and SCI. A42 and p-tau also involved in the pathogenesis of other types of dementias. In this study, we investigated the correlation between AD CSF biomarkers and grey matter (GM) volume and brain microstructural changes using Voxel-Based Morphometric (VBM) analysis and Diffusion Tensor Imaging (DTI) measurement.

Materials and Methods:

A total of 95 subjects were studied, including 21 AD, 35 MCI, 22 SCI and 17 other dementia (OD) patients. All participants underwent lumbar puncture and CSF biomarkers of A42, p-tau and T-tau were measured. All MRI image datasets were acquired on a Siemens whole-body clinical MRI 3T scanner equipped with 32-channel head coil. The MRI protocol included a high-resolution sagittal 3D T1-weighted image (T1WI) acquired with MPRAGE sequence, TR/TE=1900/2.57ms, 176 sagittal slices, voxel size 1×1×1mm^3, and flip angle=9. DTI were obtained using a spin-echo EPI sequence (TR/TE=5200/91ms, 42 axial slices, voxel size 2×2×3.6mm^3) with 30 orientations for the diffusion-sensitizing gradients b-value of 1000mm*s^{-2}. T1WI and DTI data analysis were performed using VBM and TBSS protocol with FSL (http://www.fmrib.ox.ac.uk/fsl/) respectively. For brain GM volume analysis, T1WI images were segmented into GM, white matter and CSF, and co-registered to the MNI template. GM images were smoothed using a 9-mm full-width at half maximum Gaussian kernel. The main steps for DTI analysis included: 1) correction for motion and eddy current distortion; 2) calculation of individual mean diffusivity (MD) and fractional anisotropy (FA) maps; 3) transformation of all MD and FA maps to MNI template. After pre-processing, smoothed GM images, FA and MD maps for each subject were entered into a voxel-wise permutation-based (5000 permutations) inference using randomize program with FSL to calculate the correlation with CSF A42, T-tau, p-tau, ratio of A42/p-tau and A42/T-tau respectively, adjusted for age and gender. For FA and MD data, we used the threshold mean FA map (mean value of 0.15 to include white matter and part grey matter) as a mask. The output contained statistical maps corrected for multiple comparisons at the cluster level (cluster-forming threshold $t > 2.6$, $p < 0.05$).

Results: The demographic and clinical data are shown in Table 1. VBM for the whole sample revealed positive correlation between GM volume and A42, A42/p-tau and A42/T-tau, negative correlation with T-tau (Fig.1), adjusted by age and gender. There is no significant correlation between GM volume and p-tau. Higher FA was only related to higher A42 (Fig. 2). MD showed significant positive correlation with p-tau and T-tau, and negative correlation with A42, A42/p-tau and A42/T-tau in frontal, temporal, occipital and parietal lobe (Fig. 3). In particular, subjects with higher level of A42/T-tau presented increased GM volume (Fig.1C) and lower MD (Fig.3E) in widespread area, including frontal, temporal and parietal lobe, mainly from left hemisphere.

Discussion and conclusions: The results reveal that both GM volume and brain microstructural changes in AD are related to CSF biomarkers. Interestingly, the majority of regions are consistent with amyloid deposition in the brain using positron emission tomography (PET) and overlap with the default mode network (DMN) [2], which is related to cognitive changes. Moreover, our results support that AD pathology change is more severe in the left hemisphere than right at the early stages of AD [3]. In summary, our findings suggested that the early pathological changes in AD could be detected with VBM and DTI measurement. This investigation is beneficial to further understanding of the relationship of CSF biomarkers and brain structure changes at different stages of AD. It may help us to better understand the AD pathology progression and diagnose AD at an early stage.

References: [1] *Lancet*, 368:387–403, 2006. [2] *PNAS*, 98:676–82, 2001. [3] *Arch Neurol*, 46:146–152, 1989.

Table.1 Demographic of subjects

	AD (n=21)	MCI (n=35)	SCI (n=22)	OD (n=17)
Age	65.6±7.1	60.3±9.4	56.6±8.1	59.3±8.1
Gender (M/F)	8/13	17/18	8/14	12/5
MMSE	22.3±5.2	26.4±2.8	27.6±2.5	23.0±4.0
A42	483.8±130.8	826.1±344.3	1089.2±306.0	935.4±258.8
p-tau	88.9±32.9	58.8±24.5	51.8±19.8	43.8±14.2
T-tau	634.7±275.9	357.3±200.7	277.1±125.3	248.5±103.3
A42/p-tau	6.5±4.5	17.8±11.2	22.8±6.5	24.2±10.4
A42/T-tau	1.0±0.8	3.4±2.4	4.4±1.5	4.4±1.9

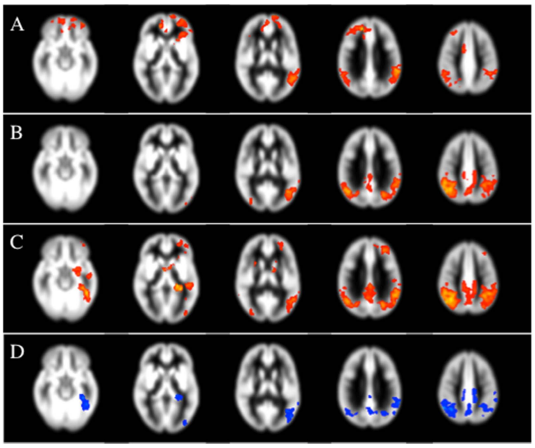

Fig.1 Results for correlation between GM volume and CSF biomarkers. GM volume showed positive correlation with A42 (A), A42/p-tau (B) and A42/T-tau (C), and negative correlation with T-tau (D), adjusted by age and gender.

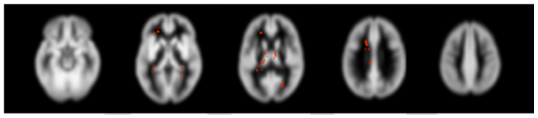

Fig.2 FA showed a positive correlation with A42, adjusted by age and gender.

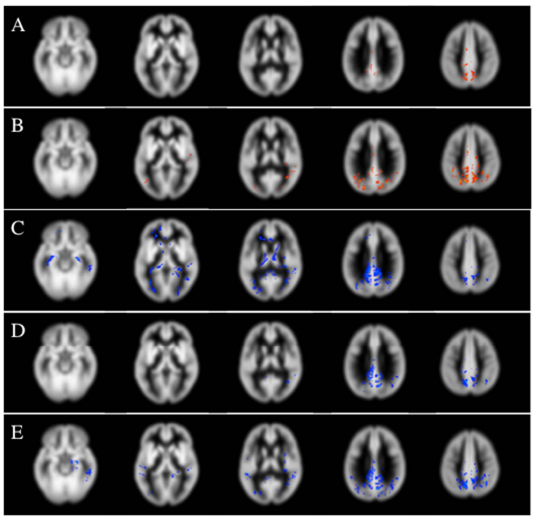

Fig.3 Results for correlation between MD and CSF biomarkers. MD showed positive correlation with p-tau (A) and T-tau (B), and negative correlation with A42 (C), A42/p-tau (D) and A42/T-tau (E), adjusted by age and gender.