

CEREBROVASCULAR DISEASE ASSOCIATED WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE

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Introduction

Cerebrovascular disease has been studied in relation to the pathogenesis and progression of Alzheimer's disease (AD) [1,2]. White matter (WM) lesions, a marker of cerebrovascular disease, have been found to be a risk factor for dementia, including AD [3,4]. Although WM changes can typically be seen as hyperintensities on T2-weighted MRI, diffusion tensor imaging (DTI) provides a tool for quantitative assessment of the integrity and changes of WM. Therefore, WM damage as the consequence of both an ischemic process as well as beta amyloid deposition may be measured by DTI for diagnosis and monitoring of AD. We report that cerebrovascular disease is closely associated with DTI measured WM changes in AD.

Methods and Subjects

The study was approved by the Institutional Review Board. Participants included 23 clinically diagnosed AD patients who were divided into 2 groups: a cerebrovascular disease group (n=11; 6 men, 5 women; age=75.2±6.1 years), and a group without cerebrovascular disease (n=12; 6 men, 6 women; age=72.9±6.9 years). Cerebrovascular disease was defined according to the presence of dilated perivascular space by signal characteristics, size, and location. In addition, 8 normal elderly subjects were included in an age-matched control group. DTI and structural MRI, including T2 weighted fast spin echo imaging and FLAIR imaging, were recorded on a Siemens Trio 3T MRI scanner. For T2 weighted fast spin echo imaging, TR/TE/angle = 25ms/2ms/30°, FOV = 224 mm, matrix = 256², slice thickness = 5 mm and no gap were used. For DTI, diffusion weighted single-shot spin echo-planar imaging (DW SSEPI) sequence with 20 diffusion sensitized gradient directions was used. Images were recorded with the isotropic pixel in the axial direction with 60 slices using 2 mm thickness without gap to cover the entire brain. The imaging parameters typically were: FOV= 224 mm, matrix of 112² (reconstructed to 224²), TR = 8.5 sec. DTI data were processed and analyzed using FSL (FMRIB, Oxford, UK). A fractional anisotropy (FA) map was calculated for each subject. Whole brain voxel-by-voxel comparison was performed in group analysis using the Tract-Based Spatial Statistics (TBSS) method implemented in FSL. TBSS offers an alternative to conventional voxelwise statistical analyses in studying multi-subject diffusion tensor imaging by using nonlinear registration algorithm followed by projection onto an alignment-invariant tract representation. Therefore, it may improve the sensitivity and objectivity of DTI analysis. Regions of interest (ROIs) were then selected from a p-value map generated by TBSS analysis following the group comparison of FAs. Since 1-p value is used in TBSS display, threshold was set at 0.95 to display the cluster or selection of ROIs with statistical significant difference within the groups. ROIs typically included frontal, temporal and parietal lobes on both hemispheres as shown in **Fig 1**. T-tests were used for comparing FA values of the ROIs in the cerebrovascular positive and negative groups. Outcomes with $P < 0.05$ were considered statistically significant.

Results and Discussions

T2 weighted fast spin echo MRI revealed that subjects in the cerebrovascular disease group typically had hyperintense signals in the bilateral parietal white matter, nucleus basalis, internal & external capsule and the lateral and medial pathways. Those lesions were frequently characterized as single or multiple small focal ischemic infarct. The sizes of the infarcts ranged from 2 mm to 10 mm. Multiple lesions or cluster of lesions were often found. Examples of the imaging characteristics of these infarcts are shown in **Fig 2**. DTI analysis indicated that AD patients exhibited lower FA values than controls in the area of the temporal lobe. When comparing FA maps of the groups with cerebrovascular disease versus without cerebrovascular disease, the group with cerebrovascular disease demonstrated statistically significant decreases in FA values in several selected ROIs. Most noticeable decreases were found in the right parietal region ($P = 0.002$), and in the left frontal ($P = 0.04$) and right frontal regions ($P = 0.085$) (**Fig 3**). FA values are particularly lower in the areas that included ischemic infarcts.

There is a considerable debate about whether AD is primarily a neurodegenerative disorder that operates in parallel with vascular changes or whether it is due solely to a vascular etiology. Cerebrovascular disease may serve to worsen or unmask the clinical symptoms of AD.

Previous studies reported that persons with cerebrovascular infarcts, especially in the basal ganglia, thalamus, and deep WM, were more likely to exhibit cognitive dysfunction and dementia than those without infarcts, despite the fact that both groups met neuropathological criteria for probable AD at autopsy. Impaired cerebral perfusion has been proposed as an etiological mechanism for non-genetic forms of AD. Our preliminary results using DTI measured WM changes may be in line with this hypothesis, but further research is necessary. Interestingly, the finding of pronounced changes in the parietal area of AD patients with cerebrovascular disease is consistent with the reports that low metabolic activity in the parietal lobes of AD patients using FDG PET. Our study further demonstrates the utility of DTI in studying AD and the potential to improve the diagnosis of this disease.

Reference: [1] Borenstein AR. *Neurobiol. Aging*, 2005. [2] Kivipelto M. *BRIT MED J*, 2001. [3] Prins ND. *Arch. Neurol.*, 2004. [4] Wu CC. *Ann NY Acad. Sci.*, 2002.

Fig 3. More significant WM changes indicated by reduction of FA values were found in AD patients with cerebrovascular disease. LT: left temporal; RT: right temporal; LF: left frontal; RF: right frontal; LP: left parietal; RP: Right parietal.

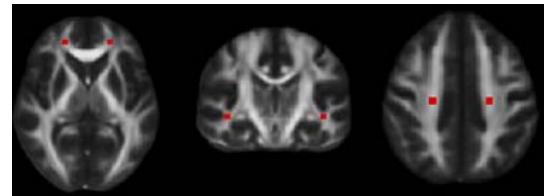


Fig 1. ROIs were selected from the FA maps of different WM areas with assistance of TBSS.

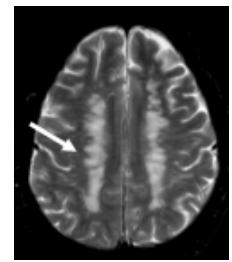


Fig 2. T2 weighted fast spin echo imaging shows the typical appearance of ischemic infarct.