

Effect of APOE4 on Partial Volume-Corrected Diffusion Anisotropy in Patients with AD and MCI®

Kyung Mi Lee¹, Min Ji Kim², Chang Woo Ryu², Ji Seon Park¹, Hak Young Rhee³, Eui Jong Kim¹, and Geon-Ho Jahng²

¹Radiology, Kyung Hee University Hospital, Kyung Hee University, Seoul, Seoul, Korea, ²Radiology, Kyung Hee University Hospital at Gangdong, Kyung Hee University, Seoul, Seoul, Korea, ³Neurology, Kyung Hee University Hospital at Gangdong, Kyung Hee University, Seoul, Seoul, Korea

Introduction: Alzheimer disease (AD) results in changes in cognitive function and cerebral structure, especially in the cortical association areas and the limbic system. In the very early stage of dementia, mild cognitive impairment (MCI) is a high risk condition for the development of clinically probable AD. Recently, some reports have shown the potential of diffusion-tensor imaging (DTI) as a useful diagnostic tool in AD and MCI (1). General reduction of fraction anisotropy (FA) and increase in trace values was found in several regions including the parietal and temporal lobes which were mostly involved in AD (2). Those DTI studies were evaluated in DTI indices without considering brain atrophy changes. Apolipoprotein E4 (APOE4) is a genetic risk factor for development of cognitive impairment and dementia. Despite of their potential importance, understanding of microstructural brain change associated with this genetic variation influences remains incomplete. The purpose of our study was to prospectively evaluate whether carriers of APOE4 were altered in brain diffusion anisotropy compared with noncarriers in AD, MCI, and cognitively normal (CN) subjects. For this investigation, we applied a partial volume correction (PVC) method of cerebrospinal fluid on FA and trace maps to test voxel-based comparisons between the carriers and noncarriers for each subject group.

Materials and Methods: 25 AD (4 men/21 women; mean age, 70.9 years; MMSE (Mini Mental State Examination Score), 17.2; APOE4, 11 noncarriers/14 carriers), 25 amnesic MCI (12/13; 67.6 years; 26.8; 20/5) and 25 CN subjects (9/16; 68.4 years; 27.3; 20/5) were enrolled in this study. There was no significant difference of demographic characteristics among groups except MMSE. For DTI data, a single-shot spin-echo echo-planar imaging (EPI) sequence was used with TR/TE=5700/78ms; SENSE factor 2.5; matrix=112 x 109; voxel=2.2 x 2.2 x 2.2 mm³; b=0 and 800sec/mm² applied along 32 diffusion-encoding directions using 3T MRI system (Philips, Achieva) equipped with an 8-channel head coil. In addition, a three-dimensional T1-weighted imaging (3D T1WI, i.e. MPRAGE) sequence was run to segment brain tissues and coregister into a standard brain template. T2-weighted and FLAIR images were also acquired to check anatomical abnormalities. The DTI index maps (FA and trace) for each subject were obtained with DTIstudioV2 software (Johns Hopkins University, Baltimore, MD, USA). Further imaging processing steps were performed with using Statistical Parametric Mapping program version 5 (SPM5, Wellcome Department of Cognitive Neurology, London, UK). Especially in the PVC step, we use following equation; corrected FA (cFA) =FA*(GM+WM) and corrected Trace (cTrace)=Trace*(GM+WM), where GM and WM are gray matter and white matter fractions obtained from the segmented 3D T1WI. In the statistical analysis, the two-sample t-test was used to compare cFA or cTrace between carriers and noncarriers for each group with covarying for subject's age and gender. In addition, one-way ANOVA was performed to compare cFA or cTrace among groups with covarying for subject's age and gender. The false discovery rate (FDR) of 5% was used with a threshold.

Results : 1) Comparisons between carriers and noncarriers for each group (Fig 1): For cFA in CN subjects, cFA in carriers reduced mainly in the left medial frontal gyrus and WM as compared with noncarriers. In MCI subjects, cFA in carriers decreased in the left precentral gyrus, WM and left posterior cingulate. cFA in carriers increased in the left corpus callosum. Finally, in AD subjects, cFA in carriers significantly decreased in the right inferior frontal gyrus, right cingulate gyrus and left lingual gyrus as well as WM. cFA in carriers increased in the right superior parietal lobule, left precuneus and left cingulate gyrus as well as WM. For cTrace in CN subjects, cTrace value in carriers was not significantly increased, but significantly decreased compared with noncarriers. In MCI subjects, cTrace value in carriers was increased in the left middle frontal gyrus. In AD subjects, cTrace value in carriers was significantly increased in the left lingual gyrus and right thalamus, but decreased in mainly frontal and temporal lobes compared with noncarriers.

2) Comparisons cFA and cTrace between groups (Fig 2): cFA in CN increased in the both frontal and right parietal lobe as compared with MCI and in MCI increased in the both parietal lobes. cFA in CN increased in the both frontotemporoparietal lobes as compared with AD and in AD increased in the both parietal lobes as compared with CN. cFA in MCI increased in the both temporoparietal lobes as compared with AD and in AD increased in the right parietal lobes. cTrace in CN increased in the right parietal cortex as compared with MCI. cTrace in AD increased in the mainly both temporoparietal lobes as compared with CN. cTrace in AD increased in the mainly both parietal lobes as compared with MCI.

Discussions: This paper is the first application of the PVC method in analyzing DTI indices in AD and MCI subjects. In addition, there is limited study in investigating DTI data on concerning the effect of the APOE genotype in AD and MCI subjects. The main finding of this study was significant changes of cFA and cTrace values in specific brain regions in APOE4 carriers as compared with noncarriers. Those changes are different as compared data without considering the partial volume correction. It is suggested that non-corrected trace values may reflect brain atrophy rather than actual tissue changes in brain parenchyma. On the microstructural level, intravoxel partial voluming would be higher in elderly subjects compared with young subjects, resulting in higher trace and reflecting age-related increased in interstitial fluid. Many previous studies demonstrated the importance of PVC in brain perfusion with using gray matter tissue (3). We suggested that applications of the PVC in analyzing DTI data in cognitive decline patients should be helpful to evaluate microstructural changes in brain.

Conclusion: Regional microstructural changes of brain in APOE4 carriers of AD and MCI subjects were confirmed by using the PVC method of DTI data for the first time. The result of this study demonstrated that the partial volume correction of cerebrospinal fluid in DTI data is very important for accurate evaluation of microstructural changes in cognitive decline patients.

Acknowledges: This research was supported by a grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A092125).

References: (1) Chua TC, et al. Curr Opin Neurol 2008;21:83-92;(2)Scola E, et al. J Neurol Neurosurg Psychiatry 2010;81:798-805;(3) Nathan AJ, et al. Radiology 2005;234:851-859

Fig 1. Increased cFA value in AD subjects noncarrier (red) vs. carrier (blue)

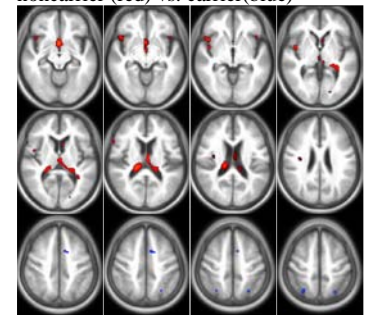


Fig 2. Increased cFA value in CN (red) vs. AD (blue)

