

Regional CBF in Patients with AD and MCI: Effect of Apolipoprotein Epsilon4 Allele

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Introduction: The apolipoprotein E (APOE) ϵ allele is the strongest genetic risk factor for AD [1,2] and is associated with cognitive impairment in elderly normal subjects [3]. All APOE isoforms inhibit amyloid beta protein aggregation, but APOE $\epsilon 4$ is less effective than APOE $\epsilon 3$ [4,5]. A few studies reported associations between rCBF and the APOE ϵ allele in groups with AD and/or MCI. Previous SPECT (single photon emission computed tomography) study showed that APOE $\epsilon 4$ carriers had significantly reduced rCBF in the right frontal and left occipital lobes in AD [6]. The main purpose of our study was to prospectively evaluate the effect of APOE genotype on rCBF in CN, MCI and AD groups. After we obtained APOE genotype information, all subjects were divided into carrier and noncarriers of the epsilon4 allele. Pulsed arterial spin-labeling (PASL) perfusion MRI was obtained to map cerebral perfusion in these subjects.

Materials and Methods: Our institutional review board approved this study and informed consent was obtained from all participants. All participants provided a detailed medical history and underwent a neurologic examination, laboratory testing, standard neuropsychological testing and MRI scan. We enrolled 75 age-matched subjects consisting of 25 elderly CN subjects, 25 subjects with amnesic MCI and 25 subjects with mild or probable AD. After the neuropsychological battery examination and before the MRI scan, blood samples were taken from all subjects to determine APOE ϵ genotypes by a restriction enzyme polymerase chain reaction technique. Subjects were then divided into three classifications, depending on the APOE $\epsilon 4$ allele including E2/E3, E3/E3 and E3/E4 to identify carriers and noncarriers with this risk factor for AD. There were no subjects with the E4/E4 allele. MR imaging was performed on a 3.0-T MR system (Achieva, Philips Medical Systems). For PASL data, the pulsed star labeling of arterial regions (PULSAR) method was used for labeling arterial blood [7] with T1=700 ms, the post-labeling delay time=800 ms, and T2=1700ms. After being calculated in CBF maps, imaging processing was performed with the statistical parametric mapping-version 5 (SPM5) program. In order to correct the partial volume effect in rCBF maps, the 3D T1-weighted image was used. rCBF differences between carriers and noncarriers of the APOE $\epsilon 4$ alleles for each subject group were investigated by voxel-wise two-sample t-test with subject age and gender as a covariate.

Results :

In the CN group, rCBF of the carrier group compared with the noncarrier group was significantly reduced in the left middle temporal gyrus, right insula, right caudate, right precentral gyrus and right inferior parietal lobule. There was no significantly increased area of rCBF in the carrier group compared with the noncarrier group. **In the MCI group,** rCBF in the carrier group compared with the noncarrier group was significantly *increased* in the right posterior cingulate, bilateral cingulate gyri, right parahippocampal gyrus, right cuneus and right lingual gyrus. There was no significantly decreased area of rCBF in the carrier group compared with the noncarrier group. **In the AD group,** rCBF in the carrier group compared with the noncarrier group was significantly reduced in the bilateral middle temporal gyri, bilateral caudate, left insula, left anterior cingulate, right claustrum, left postcentral gyrus and right inferior frontal gyrus. In addition, rCBF in the carrier group compared with the noncarrier group was significantly *increased* in the right superior frontal gyrus.

Discussions:

We demonstrated cerebral perfusion changes in patients with AD and MCI when compared to CN subjects. Carriers of the APOE $\epsilon 4$ allele in the AD group significantly decreased rCBF in several regions of brain compared with noncarriers. Carriers of the APOE $\epsilon 4$ allele in the MCI group significantly increased rCBF compared with noncarriers. CBF measurements may be important for investigating disease progression of MCI and developing high risk patients. We also demonstrated patterns of hypoperfusion in subjects with AD and MCI compared with CN subjects in several areas of the brain and these findings were consistent with previous findings [8]. In the AD group, we demonstrated patterns of hypoperfusion in the carrier group compared with the noncarrier group in several areas of the brain. In the CN group, we also found significant hypoperfusion in the APOE $\epsilon 4$ carrier group compared with the noncarrier group in several areas in brain. To our knowledge, little is known about the change of rCBF in CN and MCI subjects. Our results may suggest minimal functional changes and an increased risk of developing cognitive impairment. In the MCI group, we demonstrated patterns of hyperperfusion in the APOE $\epsilon 4$ carrier group compared with the noncarrier group in several areas of the brain.

Conclusion:

Cerebral hypoperfusion were observed in AD and MCI compared with CN. Carriers of the APOE $\epsilon 4$ allele in the AD group had significantly decreased rCBF in several regions of the brain compared with noncarriers. Carriers of the APOE $\epsilon 4$ allele in the MCI group significantly had increased rCBF compared with noncarriers. APOE $\epsilon 4$ allele that affects functional changes of brain represents a risk factor for Alzheimer's disease. ASL-MRI enhances the ability to detect disease stages in patients with AD and MCI.

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Fig. 1. Results of alterations in CBF between carrier and noncarriers in normal (A), MCI (B), and AD (C) subjects.

