Apolipoprotein E ε4 genotype is associated with the changes in cortical thickness and CSF biomarkers in mild cognitive impairment and Alzheimer's disease

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Introduction: Apolipoprotein E (ApoE) gene is mapped on chromosome 19 with 3 alleles (ε2, ε3 and ε4) (1). It is well reported that having at least one ApoE ε4 allele is the known risk factor for Alzheimer's disease (AD) and associated with the greater amyloid deposition and other neurological disorders (1, 2). Subjects heterozygous for ε4 experience three-fold increase in risk for sporadic AD, and those homozygous for ε4 allele have 12-18 fold higher risk. Various structural and functional neuroimaging modalities have been used to measure the brain's tissue changes in mild cognitive impairment (MCI) and AD patients. In the current study, we measure the cortical thickness and CSF biomarkers (beta- amyloid 42, Total-tau and Phosphorylated-tau) in MCI and AD patients who carry or lack ApoE ε4 allele. We also look for the any association between CSF biomarkers and cortical thickness in these patient groups.

Materials and methods: This study was performed under an approved Institutional study protocol. With informed consent, 16 controls, 16 MCI and 25 AD patients (table 1) underwent for a clinical assessment including Mini-mental state examination **(**MMSE**)** and a brain MRI on a 1.5-T clinical MR scanner (Siemens Medical Systems, Malvern, PA, USA). MR imaging including T2- and T1-weighted imaging and high-resolution T1-weighted 3D volumetric MPRAGE imaging with following parameters: TR/TE = 3,000 ms/3.5 ms, slice thickness = 1.2 mm, number of slice=160, FOV of 240×240 cm^2 and 192 phase encode steps, and flip angle = 8° were performed on each subject. Both T1- T2-weighted images were examined for any gross brain pathology, such as cysts, tumors, or any other mass lesions and presence of such anomaly was used as an exclusion criteria. We used high-resolution T1-weighted structural images for measuring regional cortical thicknesses in all subjects using FreeSurfer (v. 5.3.0), as described elsewhere (4). All processed data were manually-evaluated and regional changes in cortical thicknesses between patients and control subjects were examined using a vertex-by-vertex general linear model, implemented in FreeSurfer. The statistical parametric maps with regional cortical thickness differences between patient groups and control group were generated separately for left and right hemispheres. The CSF biomarkers were measured as described previously (5).

Table 1: Demographic, clinical and CSF characteristics of ApoE ε4 carriers and non-carriers.

Variables	Control		MCI		AD	
	ε4 – (8)	ε4 + (8)	ε4 – (8)	ε4 + (8)	ε4 – (11)	ε4 + (14)
Mean age (SD), years	66±6.5	66±7.6	67±5.4	68±4.0	71±9.3	74±7.6
Women/Men	7/1	3/6	5/3	5/3	7/4	8/6
Mean MMSE	29±0.9	28±1.2	26±2.8	25.4±	20±6.0	23±4.0
Luminex T-Tau (pg/ml)	46±21	59±39	45±29	85±32	108±72	114±59
Luminex P-Tau (pg/ml)	23±12	34±18	15±12	46±18	36±25	44±21
Luminex Aβ1-42 (pg/ml)	241±35	199±53	247±35	138±37	165±58	137±40

Results: No significant difference in age and gender was observed across the groups. In MCI reduced cortical thickness were observed in bilateral frontal, parietal and temporal regions, and unilateral left bankssts, insular cortex, cingulate, parsorbitalis, pre central, supramarginal and right para central, post central, and pre cuneus area (Fig 1. a and b) compared with those in controls. On comparing with controls AD showed reduced cortical thickness in following brain areas: bilateral bankssts, frontal, parietal, temporal, fusiform, insular cortices, cingulate, and supramarginal. Unilateral left includes pre and post central, and unilateral right includes cuneus, entorhinal, pericalcarine, and pre cuneus areas (Fig 1. e and f). MCI with ApoE ε4 carriers showed reduced cortical thickness in bilateral frontal, parietal, pre cuneus, and supramarginal area and unilateral left temporal, insula, parsorbitalis, cingulate, and unilateral right lingual areas (c and d) compared with those in non-carriers. Similarly, AD patients with ApoE ε4 carriers depicted reduced cortical thickness in bilateral frontal, parietal, pre cuneus, and supramarginal, and unilateral left temporal, insula, parsorbitalis, and cingulate, and unilateral lingual (g and h) areas compared with those in non-carriers. Difference in luminex Aβ1-42 between MCI with ApoE ε4 carriers and MCI non-carriers showed a significant correlation with the cortical thickness in left post central, right pre central and caudal middle frontal areas (Fig. 2).

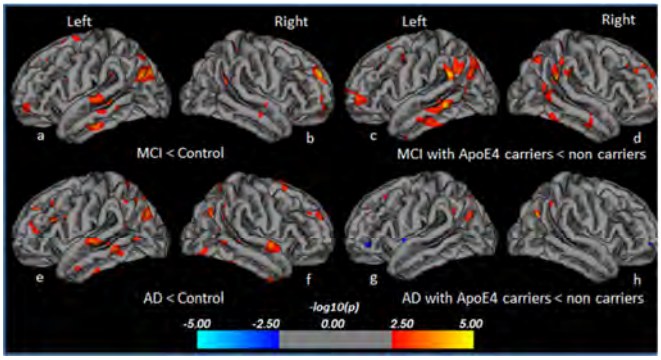

Fig. 1: Brain regions with reduced cortical thickness in MCI (a, b) and AD (e, f) compared to control subjects. MCI (c, d) and AD (g, h) with ApoE ε4 allele carriers show reduced cortical thickness in multiple brain regions compared with non-carriers (warm color).

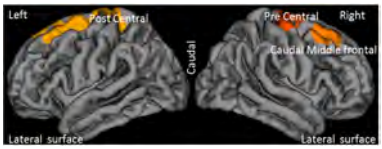

Fig. 2: MCI with ApoE ε4 allele carriers and non-carriers differences in Luminex Aβ1-42 with thickness correlation. (Scale is same as Fig. 1)

Discussion: Reduced cortical thicknesses appeared in MCI and AD in multiple brain regions, including frontal, parietal, temporal, occipital lobes. These brain areas control cognitive, autonomic, affective, language, and visual functions. MCI and AD with ApoE ε4 carriers showed greater reduction in cortical thickness than non-carriers, which suggest presence of ApoE ε4 is responsible for the higher brain's tissue damage. Pathological studies have shown significantly higher deposition of plaques and neurofibrillary tangles in brain of AD patients with ApoE-ε4 carriers than non-carriers (6). And this may be the likely explanation for more severe brain's tissue damage in ApoE e4 carriers than non-carriers.

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